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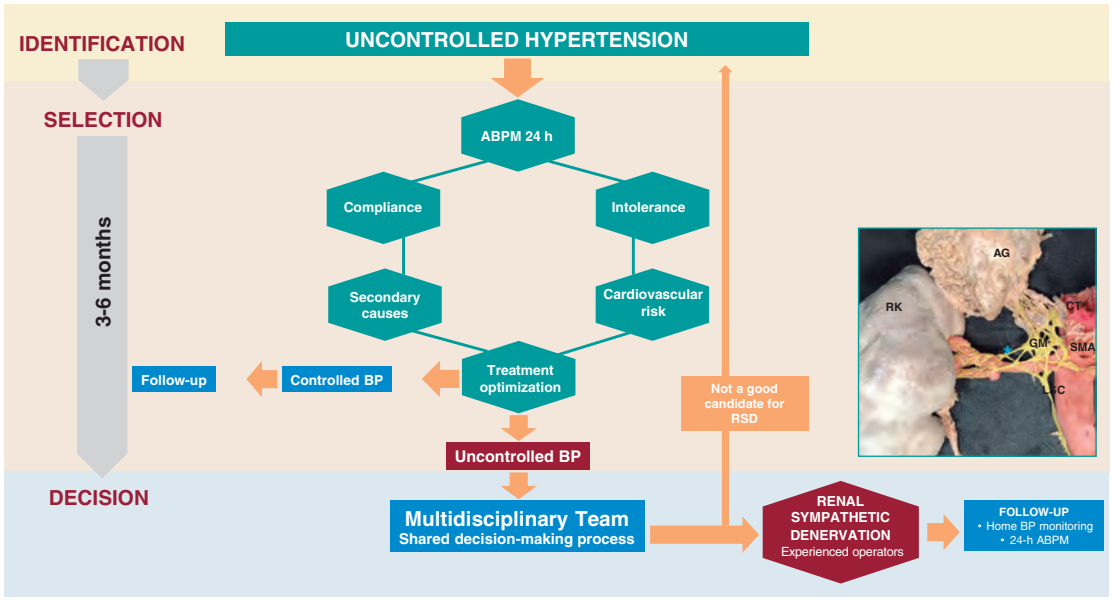
Position statement on renal denervation to treat AHT



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Editorial

Limitations of angiography in the detection of target lesion calcium. No significant differences today compared to 1995

Limitaciones de la angiografía para detectar calcificación en la lesión diana: sin diferencias significativas con respecto a 1995

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In 1995, my colleagues and I at the Washington Hospital Center (Washington, DC, United States) published an intravascular ultrasound (IVUS) vs angiographic assessment of calcium in 1155 lesions targeted for percutaneous coronary intervention (figure 1)[1]. Angiography detected calcium in 440 lesions (38%), but IVUS detected lesion calcium in 841 lesions (73%). Among these 1155 lesions, 27% had no IVUS calcium, 26% had 1-quadrant IVUS calcium, 21% had 2 quadrants, 15% had 3 quadrants, and 11% had 4-quadrant IVUS calcium. When present, target lesion calcium was only superficial in 48%, only deep in 28%, and both superficial and deep in 24%. Therefore, some superficial calcium was present in 72% of the 841 calcium-containing lesions (1-quadrant superficial calcium in 35%, 2 quadrants in 31%, 3 quadrants in 18%, and 4-quadrant superficial calcium in 18%). The diagnostic ability of angiography to detect calcium was primarily dependent on the arc and length of calcium, but also on whether calcium was or not superficial (figure 1). However, there was also a curious 10% rate of angiographic false positives attributed to the difficulty differentiating perivascular or reference segment calcium from intralesional calcium. However, it was never clear whether there was a systematic problem with angiographic calcium detection or whether it was because, in the early 1990s, angiography was primitive compared to today and would improve over time.

This experiment was repeated more than 20 years later by Wang et al. in a smaller cohort of 440 lesions using state-of-the-art angiographic equipment and both IVUS and optical coherence tomography (OCT) imaging (figure 1).[2] Any amount of calcium was detected by coronary angiography in 40.2% (177 of 440) of the lesions, by IVUS in 82.7% (364 of 440) of the lesions, and by OCT in 76.8% (338 of 440) of the lesions. Notably and compared to the 1995 study, almost all calcium was superficial, fewer lesions had no calcium, and more lesions had 1- or 2-quadrant calcium (figure 1). In 13.2% of the lesions with IVUS-detected calcium, calcium was not visible by OCT mostly because of attenuation due to superficial lipid plaque accumulation. In a recent paper published in *REC: Interventional Cardiology*, McGuire et al.[3] compared angiographic vs OCT calcium detection in 75 lesions. OCT detected calcium in 69 lesions vs 30 lesions by angiography with no angiographic false positives (figure 1).[3] Compared to IVUS, OCT can measure the thickness, area, and volume that affect the angiographic detection of calcium in addition to its arc and length.[2,3]

Other than a reduced rate of false positives in the 2 contemporary studies, which could be attributed to the improved resolution of modern x-ray equipment, the lower x-ray doses being used today vs 1995, and the clinical recognition of the existence perivascular calcium, the results were remarkably similar to those of 1995. Thus, there appears to be a fundamental limitation to x-ray that cannot be improved by technological advances.

Why is calcium detection so important? The primary cause of in-stent restenosis is stent underexpansion, the primary cause of stent underexpansion is calcium, and the natural history of in-stent restenosis is not benign with an annual mortality rate of 5% to 7% (associated with treatment and at the follow-up).[4-7] There are calcium scores for both OCT and IVUS that reliably predict calcium-related stent underexpansion (figure 2);[8,9] and there are technologies and approaches that can be used to modify calcium to promote a better stent expansion.[4,10]

There are predictors of target lesion calcium at patient level (older age, non-insulin treated diabetes, stable angina rather than an acute coronary syndrome, chronic kidney disease—especially if a patient is on dialysis—, and calcium elsewhere in the coronary tree), and predictors at lesion level too (smaller vessels, more severe stenoses).[11-15] However, for the most part, lesions behave independently with regards to calcium accumulation. Only intravascular imaging can reliably detect and quantify target lesion calcium and predict stent underexpansion in the severe target lesion calcium setting.

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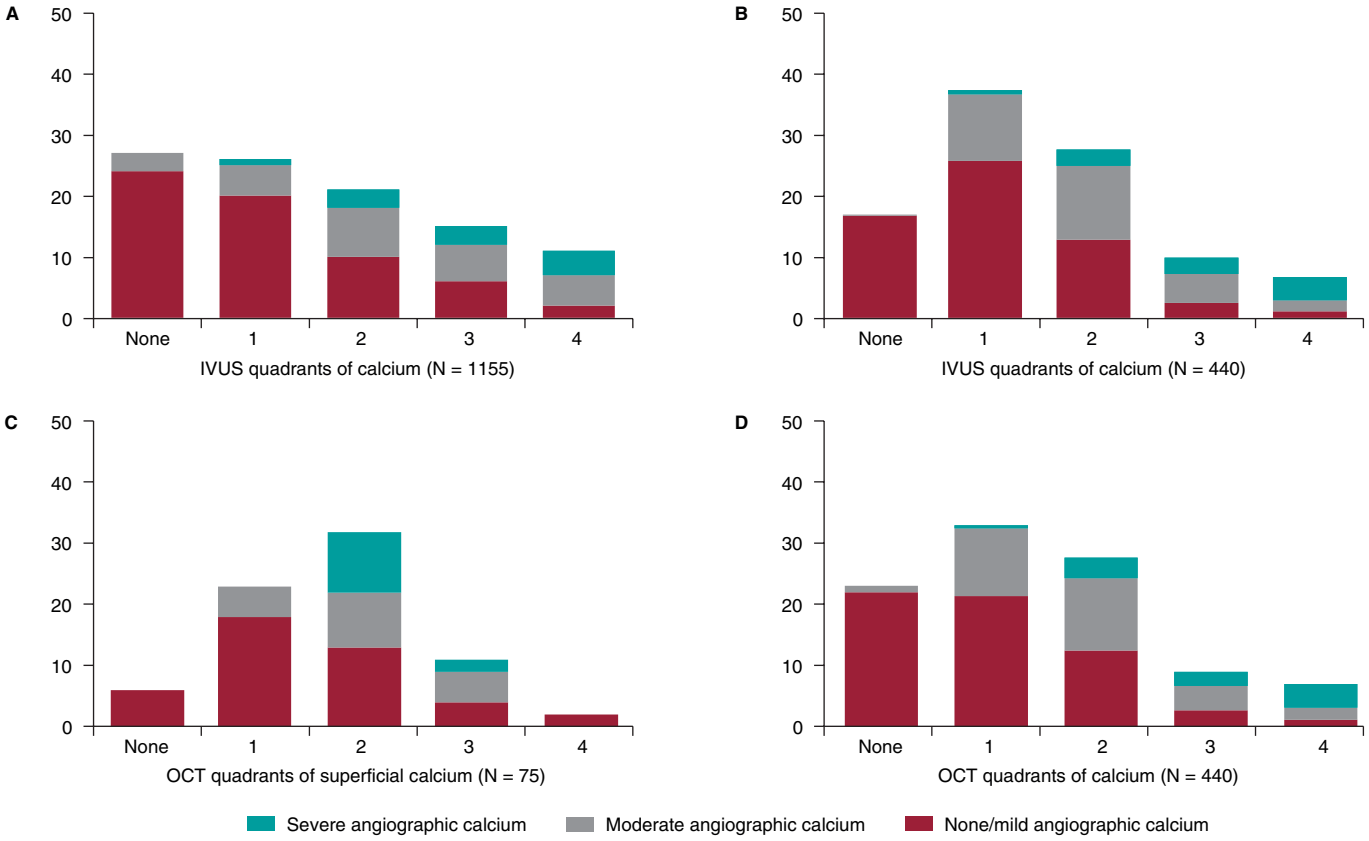

Figure 1. A total of 3 studies (clockwise starting in the upper left-hand corner) comparing intravascular imaging to the angiography detection of coronary lesion calcium. **A:** the study conducted by Mintz et al.[1] from 1995. **B** and **C:** the study by Wang et al.[2] from 2017. **D:** the study by McGuire et al.[3] from 2021. IVUS, intravascular ultrasound; OCT, optical coherence tomography.

IVUS calcium score predicting stent expansion in lesions with calcium > 270°

	Calcium Score	
Length of calcium > 270° (per 5 mm)	≤ 5 mm	0
	> 5 mm	1
Calcium nodule	Absent	0
	Present	1
Vessel diameter (per 1mm)	> 3.5 mm	0
	≤ 3.5 mm	1
Circumferential calcium	Absent	0
	Present	1
Stent underexpansion defined as < 70%		
Calcium score cut-off	≥ 2	
C-statistics	0.85 [0.77, 0.93]	
Sensitivity	89%	
Specificity	63%	
Positive predictive value	48%	
Negative predictive value	94%	

OCT calcium scoring system predicting stent expansion

	Calcium Score		
Maximum calcium angle (per 180°)	Maximum calcium angle	≤ 180°	0
		> 180°	2
Maximum calcium thickness (per 0.5 mm)	Maximum calcium thickness	≤ 0.5 mm	0
		> 0.5 mm	1
Calcium length (per 5 mm)	Calcium length	≤ 5 mm	0
		> 5 mm	1
Calcium score	Stent expansion at lesion calcium, %	Stent expansion at MSA, %	
0	99 (93, 108)	91 (84, 95)	
1	98 (86, 109)	85 (78, 93)	
2	86 (77, 100)	80 (73, 93)	
3	98 (83, 104)	80 (73, 85)	
4	78 (70, 86)	69 (60, 77)	

Figure 2. Intravascular ultrasound and optical coherence tomography calcium scores to predict stent underexpansion.[8,9] IVUS, intravascular ultrasound; MSA, minimum stent area; OCT, optical coherence tomography.

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Editorial

Small margins and big gains: evidence for angioplasty with cutting or scoring balloons in patients with in-stent restenosis

Pequeños márgenes y grandes ganancias: evidencia sobre la angioplastia con balones para la modificación de la placa en la reestenosis intrastent

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The use of drug-eluting stents (DES) for the treatment of coronary artery stenosis substantially reduced the need for repeat revascularization compared to bare-metal stents.[1] However, as many patients undergoing stenting have long life expectancy, and the incidence rate of stent failure increases with time since implantation, the number of patients presenting with DES restenosis is not insignificant and the treatment of these patients remains a challenge.[2]

Current clinical practice guidelines recommend treatment of restenosis associated with angina or ischemia by repeat revascularization with either repeat stenting with DES or angioplasty with drug coated balloon (DCB).[3] Certain situations favour repeat stenting with DES, most notably loss of mechanical integrity of the restenosed stent. In general, however, although repeat stenting with DES may be more effective than angioplasty with DCB in the short-to-medium-term,[4] avoidance of additional stent layers is an important consideration in the longer-term. Indeed, many centres prefer DCB angioplasty as a first-line approach for the treatment of restenosis in the absence of a compelling indication for repeat stenting.

The efficacy of DCB treatment relies on rapid transfer and subsequent tissue retention of the anti-proliferative agent, which is necessary for a persistent suppression of cell proliferation.[5] Preclinical data suggest that micro-injuries to the vessel wall may enhance the ability of DCBs to inhibit neointimal growth.[6] These micro-injuries can be achieved with a number of different types of modified balloon catheters, such as cutting or scoring balloons. Cutting balloon angioplasty is an attractive option thanks to its ability to effectively incise neointimal tissue and its ease of use.[7] Scoring balloons are based on the same principle and may offer superior flexibility and deliverability at the expense of a somehow lower plaque disruption.

In a recent paper published in *REC: Interventional Cardiology*, Linares Vicente et al. reported on the 5-year results of cutting or scoring balloon angioplasty combined with DCB to treat in-stent restenosis.[8] A total of 51 lesions (42 patients) were treated with cutting balloons plus DCBs, and 56 lesions (49 patients) with a standard DCB angioplasty. Both the SeQuent Please (B. Braun Melsungen AG, Germany), and the Pantera Lux (Biotronik, Switzerland) balloons were used. The primary endpoint was clinically driven target lesion revascularization at 5 years. It appears that, compared to the standard DCB strategy, the use of cutting or scoring balloons considerably reduced the 5-year rate of target lesion revascularization, although this difference was not statistically significant (9.8% vs 23.6%; odds ratio = 0.36; 95% confidence interval, 0.19-1.09; $P = .05$) (figure 1).

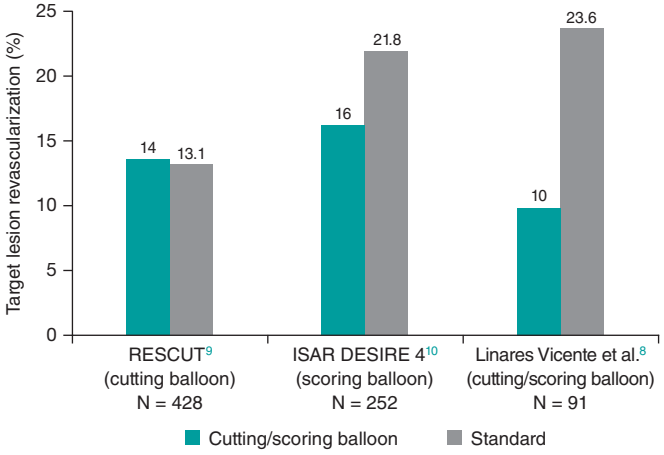

Figure 1. Target lesion revascularization (%): studies comparing cutting balloon/scoring balloon vs standard therapy in patients treated with percutaneous intervention for in-stent restenosis.

The study was retrospective and conducted at a single center with a small sample size of 91 patients. However, it is representative of real-world evidence, which may reflect clinical experiences across a broader and more diverse population of patients than those enrolled in randomized controlled trials. Regarding the baseline characteristics, almost 85% of patients were men with a mean age of 68.3 years. Patients had a high prevalence of diabetes mellitus and smoking (36% and 59%, respectively).

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Interestingly, despite the current recommendations of the European Society of Cardiology,[3] the use of intravascular ultrasound or optical coherence tomography was relatively low (5.9% in the cutting balloon group, and 8.9% in the standard group). Although this is consistent with rates observed in surveys of use in the clinical practice,[11] it represents a missed opportunity for the mechanistic understanding of the disease etiology, and guidance for treatment optimization.[12]

The primary endpoint was the need for clinically driven target lesion revascularization at 5 years, which was 64% lower with cutting or scoring balloon angioplasty. Given the small sample size of this study and the relatively large treatment effect, it is a pity that insights from the angiographic follow-up were not available. Concordant data from systematic surveillance angiography would have given more confidence to the robustness of the observed treatment effect.

The results of this study should be interpreted in the context of earlier randomized controlled trials with cutting or scoring balloon angioplasty. In fact, evidence from such trials is scant including the RESCUT (Restenosis cutting balloon evaluation trial) trial[9] published in 2003, and the more recent ISAR DESIRE 4 (Intracoronary stenting and angiographic results: optimizing treatment of drug-eluting stent in-stent restenosis 4) trial.[10]

In RESCUT, Albiero et al. randomized 428 patients with bare-metal stent in-stent restenosis across 23 European centers to receive either cutting balloon angioplasty or conventional balloon angioplasty.[9] Overall, the trial showed neutral results: at late follow-up, the angiographic restenosis rate, minimal lumen diameter, and the rate of clinical events were similar in both arms (figure 1). Cutting balloon angioplasty, however, was associated with some important procedural advantages, such as use of fewer balloons, less requirement for additional stenting, and a significantly lower incidence of balloon slippage (6.5% vs 25%).

ISAR DESIRE 4 was a randomized, open-label, assessor-blinded trial that enrolled 252 patients with clinically significant DES restenosis undergoing DCB angioplasty at 4 different centres in Germany.[10] This trial investigated scoring balloon rather than cutting balloon angioplasty. The primary endpoint–diameter stenosis at the 6-8-month follow-up angiography–was lower for the scoring balloon compared to the regular balloon angioplasty: 35% vs 40.4%; P = .047; in addition, target lesion revascularization was numerically lower (figure 1). Although, the size of treatment effect was modest, small incremental gains in efficacy in this challenging patient subset may translate into important clinical benefits.

Against this background, the observations made by Linares Vicente et al.[8] are an important addition to the evidence supporting the clinical use of cutting or scoring balloons to treat stent failure. While repeat stenting with DES or angioplasty with DCB are the mainstay of in-stent restenosis procedures, the procedural efficiency and clinical efficacy of both approaches will likely improve with the adjunctive use of cutting or scoring balloons. The benefits of these devices are most likely mediated by a combination of factors: reduced balloon slippage (or watermelon-seeding), the mechanical advantage of increased disruption of restenotic tissue, and the potential for enhanced efficacy of the device-delivered drug. The management of patients with stent failure remains challenging and deserves the best treatment the operator can offer including the liberal use of cutting or scoring balloon lesion preparation. In this clinical setting, small margins can make a big difference.

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CONFLICTS OF INTEREST

R.A. Byrne declared research or educational funding in the institution he currently works at from Abbott Vascular, Biosensors, Biotronik, and Boston Scientific. L. McGovern declared no conflicts of interest whatsoever.

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Original article

Comparison of quantitative calcium parameters between optical coherence tomography and invasive coronary angiography

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ABSTRACT

Introduction and objectives: Former studies have associated the severity of calcified plaques (CP) on the invasive coronary angiography (ICA) with a limited number of optical coherence tomography (OCT) measurements. The objective of this study was to describe the correlation between an extended and comprehensive set of OCT measurements and the severity of calcifications as seen on the ICA.
Methods: We retrospectively studied 75 patients (75 lesions) who underwent ICA and, concurrently, OCT imaging at a single institution. The OCT was performed before the percutaneous coronary intervention and after the administration of intracoronary nitroglycerine. The coronary artery calcium was scored using a three-tier classification system on the ICA. Maximum calcium angle, area, maximum thickness, length of calcium, and calcium depth were assessed on the OCT.
Results: The ICA detected fewer CP lesions compared to the OCT (N = 69; 92%), all cases of positive ICA were detected by the OCT (N = 30; 100%). The OCT did not find any positive lesions in negative angiographic lesions (N = 6; 100%). The sensitivity of the ICA was 43.5% (95%CI, 0.32-0.56) and its specificity, 100% (95%CI, 0.52-1.0). In most cases, as calcium angle, thickness, and area increased on the OCT so did the calcium severity of the lesions on the angiography.
Conclusions: Compared to the OCT, the ICA has a low sensitivity and a high specificity in the detection of calcified plaques. As calcium angle, thickness, area, and length increased on the OCT so did the number of angio-defined lesions of severe CP.

Keywords: Tomography. Optical coherence tomography. Invasive coronary angiography. Percutaneous coronary intervention. Calcification.

Comparación de parámetros cuantitativos de calcio por tomografía de coherencia óptica y angiografía coronaria invasiva

RESUMEN

***Introducción y objetivos*:** Estudios previos han asociado la gravedad de la calcificación de las lesiones coronarias evaluadas con angiografía coronaria invasiva (ACI) con un número limitado de medidas obtenidas con tomografía de coherencia óptica (OCT). El objetivo de este estudio es analizar la correlación de una amplia y exhaustiva serie de medidas de OCT con la gravedad de la calcificación estimada por ACI.
***Métodos*:** Se estudiaron retrospectivamente 75 pacientes (75 lesiones) de un único centro a quienes se realizaron simultáneamente ACI y OCT. La OCT se llevó a cabo tras la administración de nitroglicerina intracoronaria antes del intervencionismo coronario. En la ACI, la calcificación coronaria se valoró utilizando un sistema de clasificación en tres grados. Con OCT se evaluaron el máximo ángulo, el área, el grosor máximo, la longitud y la profundidad del calcio.
***Resultados*:** La ACI detectó menos lesiones calcificadas que la OCT (n = 69; 92%) y todos los casos detectados por ACI fueron identificados con OCT (n = 30; 100%). La OCT no encontró calcio en ninguna de las lesiones sin calcio en la ACI (n = 6; 100%). La sensibilidad de la ACI fue del 43,5%, (IC95%, 0,32-0,56) y la especificidad del 100% (IC95%, 0,52-1,0). A medida que se incrementaron el ángulo, el grosor y el área del calcio por OCT también aumentó la gravedad del calcio determinada por ACI en la mayoría de los casos.
***Conclusiones*:** La ACI tiene una baja sensibilidad, pero una alta especificidad, para la detección de lesiones calcificadas en comparación con la OCT. Al incrementarse el ángulo, el grosor, el área y la longitud del calcio en la OCT aumenta el número de lesiones con calcificación grave en la ACI.

Palabras clave: Tomografía. Coherencia óptica. Angiografía coronaria invasiva. Intervención coronaria percutánea. Calcificación.

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Abbreviations

CP: calcified plaque. **OCT:** optical coherence tomography. **ICA:** invasive coronary angiography.

INTRODUCTION

Coronary artery disease is very prevalent in the United States and is associated with high cardiovascular mortality rates.[1] The management of advanced coronary artery disease (eg, calcified lesions) is often the percutaneous coronary intervention, but the use of the PCI alone in calcified plaques (CP) is associated with poor procedural outcomes.[2-5] This is mainly due to the lack of information on the spread of calcification and its appropriate management before stenting. Therefore, intravascular imaging modalities are necessary for the characterization of calcium inside the vessel and better guide the interventional cardiologist.[6-9]

The optical coherence tomography (OCT) is a high-resolution cross-sectional imaging modality with an unparalleled axial resolution of around 4-20 microns.[10] The OCT allows more accurate measurements of the CP over other invasive imaging modalities like the invasive coronary angiography (ICA) and the intravascular ultrasound (IVUS).[11]

Prior studies have associated the severity of the CP on the ICA with a limited number of measurements on the OCT.[6,12-14] Our study aimed to further describe the correlation between an extended and comprehensive set of OCT measurements and the severity of calcification as seen on the ICA.

METHODS

Study population

We retrospectively studied 75 patients who underwent ICA and concurrently had OCT imaging acquired at the St. Francis Hospital, Roslyn, NY, United States, from November 2018 through April 2019. A total of 109 lesions were identified in these patients on the ICA. An OCT plus an ICA analysis were performed on 75 of these lesions deemed primary lesions while 34 lesions were excluded from the analysis (no OCT available). All primary lesions were lesions seen on the OCT images, not on the target lesion that received the stent during the procedure. No severely calcified plaques that could not be catheterized were excluded. All the lesions excluded were secondary or tertiary lesions that were deemed non-primary based on the lower calcification burden. No lesions required preparation or ablation before the OCT imaging. All the calcified spots in the population were not thick enough so as to cast a shadow. An institutional review board waiver was obtained because of the retrospective nature of this study. Patient consent was obtained for both the ICA and the OCT.

Optical coherence tomography acquisition

The OCT was performed before the percutaneous coronary intervention and after the administration of intracoronary nitroglycerine (100 µg-200 µg) using the frequency-domain OCT ILUMIEN OPTIS system (Abbott Vascular, United States) and a 2.7-Fr OCT imaging catheter (C7 Dragonfly, Dragonfly Duo or Dragonfly OPTIS; Abbott Vascular, United States). An OCT catheter was advanced distally to the lesion. Also, contrast media was injected manually through the guiding catheter with automatic pullback at a rate of 20 mm/sec for an average pullback distance of 75 mm ± 12.2 mm.

Imaging definition and analysis

The ICA and the OCT imaging were co-registered with respect to each other based on each patients' anatomical landmarks. Afterwards, the co-registered ICA and OCT imaging had all identifiers removed. Both the ICA and the OCT measurements were assessed independently by two experienced angiography evaluators who were blind to the patients' information except for the data on the anatomical location of the lesion on the ICA that was assessed on 2 different projections to secure increased accuracy when looking at the vessel. The evaluators then scored the degree of calcium based on the three-tier classification system: minimal or no calcification; calcium covering ≤ 50% of the vessel circumference was classified as "moderate calcification"; calcium covering between 50% and 100% of the vessel circumference was classified as "severe calcification" according to Mintz et al. classification.[9] In case of discrepancy between the evaluators, a third evaluator blind to the information of both the patient and the independent reviewers' assessment was invited to grade the degree of calcification.

The OCT calcium analysis was performed in the pre-percutaneous coronary intervention iFR-pullbacks. All the OCT analyses of the CP were performed using the QIVUS 3.1 validation utility tool (Medis Medical Imaging, The Netherlands) based on a standardized operating procedure at the core lab (MedStar Cardiovascular Research Network). The CP was analyzed on the area of maximum severity and defined by heterogenous areas of low signal attenuation and sharply demarcated borders. We assessed all pullbacks at lesion site level: the maximum calcium angle, maximum thickness, and length of calcium (number of frames with calcium). The angle of calcium was determined using the center of the lumen as the vertex (figure 1, red rays) as it extended from one clearly delineated border of the calcium plaque to the other. Automatic software detection was used to identify the fibrous cap overlying the calcium area and the maximum and minimum depths of calcium (figure 1, area in green). We tracked down the area of calcium determined by border delineation of the heterogenous calcium plaque. Calcium thickness (figure 1, yellow line) was analyzed on the slice with the maximum angle (figure 1). The length of calcium was derived by the total number of calcium-containing slices and then multiplied by the frame interval.

Intra- and inter-rater observer reproducibility

The intra-rater variability of the ICA and the OCT imaging analysis was assessed by evaluating 24 randomly selected images of primary lesions deemed inexistent/mild, moderate, and severe by 2 independent evaluators on both the ICA and the OCT. All OCT measurements including angle, thickness, length, and area were also measured. The same 2 evaluators analyzed the same 24 ICA and OCT images 4 weeks after the early evaluation.

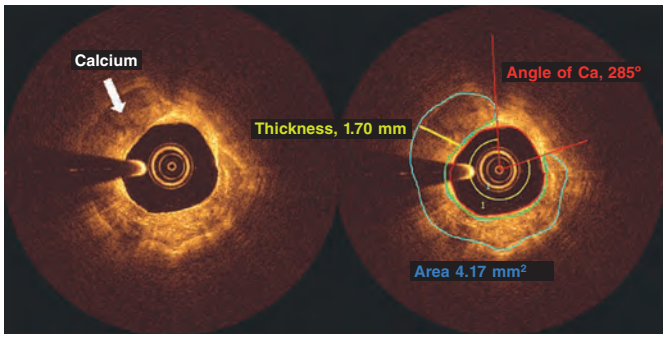

Figure 1. Optical coherence tomography frames showing a calcified plaque. The angle of calcium was determined using the center of the lumen as the vertex (red rays) and extending from one clearly delineated border of the calcium plaque to the other. Automatic software detection was used to identify the cap of the calcium plaque and the maximum and minimum depths of calcium (area in green). Calcium thickness (yellow line) was analyzed on the slice with the maximum angle after tracking down the area of calcium determined by the delineated borders of the heterogenous calcium plaque. Ca, calcium.

The inter-rater variability of the ICA and the OCT imaging analysis was assessed by evaluating 50 randomly selected images of primary lesions deemed inexistent/mild, moderate, and severe by the same 2 independent evaluators on both the ICA and the OCT. All OCT measurements including angle, thickness, length, and area were also measured. The independent evaluator analyses were then compared. Both the inter and Intra-rater reproducibility were analyzed using Cohen's kappa coefficient.

Statistical method

The comparison of all categorical variables (presented as counts and percentages) was performed using the chi-square test or Fisher's exact test. Continuous data were compared used the Student *t* test. Continuous data were expressed as mean ± standard deviation for normally distributed variables or as median (interquartile range) for non-normally distributed variables. The sensitivity and specificity of the ICA with respect to the OCT were determined using standard 2 x 2 tables. Logistic regression determined the relationship between severity as seen on the angiography and the OCT measurements. The receiver operating characteristic (ROC) analysis established the optimal cut-off values using the area under the curve and Youden's index.

RESULTS

Intra- and inter-rater observer reproducibility analysis

There was a 96% agreement (23/24; k = 0.92) on the intra-rater agreement between the analysts. This was indicative of an almost perfect inter-analysis agreement. There was only 1 case of disagreement between moderate calcification vs inexistent/mild calcification.

There was a 94% agreement (47/50; k = 0.72) on the inter-rater agreement between the analysts. This was indicative of substantial inter-rater agreement. There was disagreement between the analysts in 2 cases of moderate vs inexistent/mild calcification and in 1 case of moderate vs severe calcification.

Population

The baseline clinical characteristics of our patients are shown on table 1. Patient population was predominantly male with ages

Table 1. Patient demographics and angiographic findings

N = 75	
Age, years	65.9 ± 9.6
Male	55 (73.3)
Body height, cm	171.6 ± 11.6
Body weight, kg	92.4 ± 20.3
Creatinine levels, mg/dL	1.12 ± 0.95
Diabetes	28 (37.33)
Hypertension	59 (78.67)
Hyperlipidemia	57 (76)
Smoker	40 (53.33)
Hemodialysis	2 (2.67)
Peripheral artery disease	4 (5.33)
Previous myocardial infarction	11 (14.67)
Previous coronary artery bypass graft	4 (5.33)
Clinical presentation	
ST-elevation myocardial infarction	0 (0)
Non-ST-elevation myocardial infarction	7 (9.33)
Unstable angina	43 (57.33)
Silent ischemia	4 (5.33)
Angiographic findings	
Percutaneous coronary intervention	61 (81.33)
Femoral access site	63 (84)
Catheter Size, French	6
Target vessel	
Left main coronary artery	1 (1.33)
Left anterior descending coronary artery/Diagonal branches	61 (81.33)
Left circumflex artery/Ramus intermedius branch/Obtuse marginal	10 (13.33)
Right circumflex artery/Posterior descending artery	7 (9.59)
Lesion location	
Proximal	40 (57.14)
Mid	26 (37.14)
Distal	4 (5.71)
Lesion and stent parameters	
Lesion length, mm	25.84 ± 13.47
Lesion stenosis	74.74 ± 15.27
Stent diameter, mm	3.11 ± 0.53
Stent length, mm	24.62 ± 8.84
Pullback distance, mm	75 ± 12.2

Data are expressed as no. (%) or mean ± standard deviation.

A

	OCT (+)	OCT (–)
Angio (+)	30	0
Angio (–)	39	6
	69	6

B

	OCT (+)	OCT (–)
Angio (+)	0.43	0
Angio (–)	0.57	1
	1	1

C

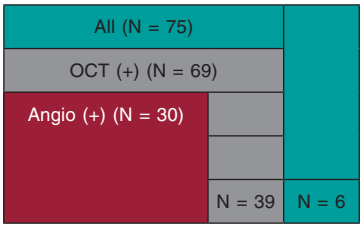

Figure 2. Calcified plaques lesions as seen on the angiography in relation to the OCT. **A:** OCT positive and negative values on the x-axis, and angio positive and negative values on the y-axis. The 4 x 4 table shows the correlation between the OCT and the angio measurements by primary lesion number. **B:** OCT positive and negative values on the x-axis, and angio positive and negative values on the y-axis. The 4 x 4 table shows the correlation between the OCT and the angio measurements by primary lesion percentage. **C:** total primary lesion numbers (in green color); the partition on the green color represents the primary lesions not found on the OCT or the angio. All OCT positive primary lesions are represented (in gray color); the partition on the gray color represents the OCT primary lesions not found on the angio. All angio positive lesions are shown (in red color); these lesions were all detected by the OCT. Angio, angiography; OCT, optical coherence tomography.

from 56.3 to 75.5. Most patients presented with unstable angina. Comorbidities were present in most of the patients being hypertension the most prevalent of all closely followed by hyperlipidemia. Smokers comprised over half of the patient population. The most common vessel imaged on the OCT was the left anterior descending coronary artery.

Angiographic severity and optical coherence tomography parameters

We examined a total of 75 lesions. The detection of CP lesions on the angiography in relation to the OCT is shown on figure 2. The angiography detected fewer CP lesions compared to the OCT that detected positive lesions (n = 69; 92%). All cases of positive angiography were detected by the OCT (n = 30; 100%). The OCT did not find any positive lesions in negative angiographic lesions (n = 6; 100%). A total of 43% of the lesions were both OCT positive and ICA positive. The ICA sensitivity was 95%CI, 0.32-0.56, and the ICA specificity, 95%CI, 0.52-1.0.

In most of cases, as the calcium angle (figure 3A), thickness (figure 3B), area (figure 3C), and length (figure 3D) increased on the OCT so did the calcium severity of the lesions on the angiography. The association between calcium severity as seen on the angiography and calcium length as seen on the OCT is shown on figure 3D. On the OCT, the severity of CP lesions run parallel to the increasing length seen on OCT.

DISCUSSION

The main findings of our study are: *a)* compared to the OCT, the ICA has a low sensitivity and a high specificity for the detection of calcium; *b)* as calcium angle, thickness, area, and length increased on the OCT so did the number of angio-defined severe CP lesions.

The ICA provides 2D real-time imaging with in-vivo characteristics of the lumen profile.[15] Conversely, the invasive 3D-OCT imaging modality has the highest resolution to characterize variations in the composition of the plaque.[11,16] The ICA detection of angiographic lesions has been used for decades. However, studies have shown that the ICA capabilities to detect calcified plaques in the arterial wall are poor.[6,11,17] Some studies have compared the ICA characterization and quantification of plaque to the coronary computed tomography angiogram and the intravascular ultrasound, but few have looked into ICA plaque characterization and quantification with the OCT.[6] Our study examined the sensitivity and specificity of ICA compared to the OCT. We examined 75 lesions and found that ICA sensitivity and specificity were 32%-56%, and 52%-100% with a 95%CI, respectively. Sensitivity was lower compared to former studies that showed a 50.9% sensitivity and a 95.1% specificity.[6] The sensitivity of ICA is low because it only provides a 2D projection of the lesion and its resolution compared to the OCT is worse.[18,19]

The OCT detected all CPs present on the ICA (n = 30) and, also, lesions that were not present on the ICA (n = 39). On the angiography, the presence of CP is indicative that calcification has large CP characteristics on the OCT (eg, angle, thickness, and area). Our study concluded that severe calcifications on the ICA are seen with higher calcium angles on the OCT as the study conducted by Wang et al proved.[6] The clinical implication of this is that when the ICA detects a calcified lesion, whether moderate or severe, the clinician can be sure that this calcification is, actually, present. The OCT would be the logical next step for a better characterization of the CP. Determining the morphology of the calcified lesion (eg, superficial, deep, or nodular) on the OCT allows selecting the optimal lesion preparation strategy. Also, the OCT detected calcifications that the ICA simply could not find, indicative that the ICA alone is not reliable to detect CPs. Therefore, with suspected lesions, the OCT should be the next step for a comprehensive assessment of these lesions.

The OCT measurements of a calcified lesion thickness, length, and area are unique to this technology because the OCT is the only invasive imaging modality capable of measuring these values.[6] Thicknesses > 0.5 mm are associated with stent underexpansion.[7,20] We did not explore this in our population since not all lesions received percutaneous coronary intervention. We did expand, however, the OCT analysis to include the depth, and area of calcium on the OCT. We found that as the area increased on the OCT so did the number of severe lesions on the ICA. We found that most severe CP lesions were in the 4.8-6 mm^2 range. Perhaps, calcium areas > 5 mm^2 may be the fourth "5" in the OCT-based "rule of five" that identifies the CP features associated with poor stent expansion.[7]

Study limitations

This was a retrospective observational study with its inherent limitations. The sample size was relatively small.

CONCLUSIONS

Invasive coronary angiography has a low sensitivity and a high specificity for the detection of calcified plaques compared to the OCT. As calcium angle, thickness, area, and length increased on the OCT so did number of angio-defined severe CP lesions.

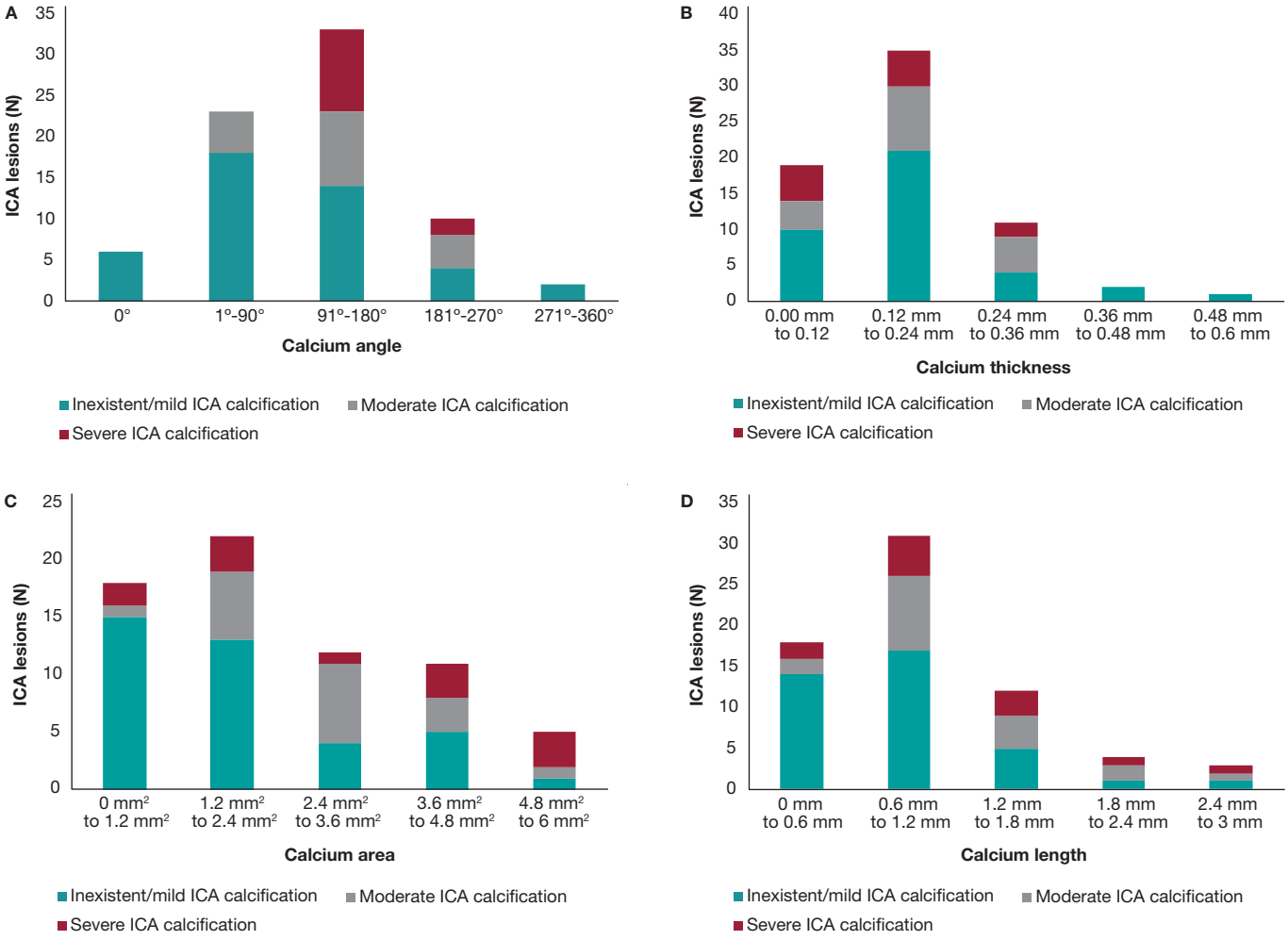

Figure 3. **A:** angiographic lesions graded by severity inside the OCT angle measurements. All values are expressed in frequencies. Angles are in ranges of equal proportions based on the degrees seen. The most severe OCT lesions were found in the 91°-180° range followed by the 181°-270° OCT angle measurement. No severe CP lesions were found in the 0°, 1°-90° OCT angle measurements. **B:** angiographic lesions graded by severity inside the OCT thickness. All lesions are expressed as frequencies. The OCT thickness is expressed in mm and distributed in ranges that go from minimum to maximum values. The highest degree of angiographic calcium score-severe CP-was equally found in 0 mm-0.12 mm, and 0.12 mm-0.24 mm thicknesses on the OCT. **C:** angiographic lesions graded by severity inside the OCT area. All lesions are expressed as frequencies. The OCT area is expressed in mm^2 and distributed in ranges that go from minimum to maximum values. The highest degree of angiographic calcium score-severe CP-was found from 4.8 mm^2 to 6 mm^2. **D:** angiographic lesions graded by severity inside the OCT length. All lesions are expressed as frequencies. The OCT length is expressed in mm and distributed in ranges that go from minimum to maximum values. The highest degree of angiographic calcium score–severe CP–was detected from 0.6 mm to 1.2 mm. CP, calcified plaques; ICA, interventional coronary angiography; OCT, optical coherence tomography.

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None.

AUTHORS' CONTRIBUTIONS

C. McGuire: study idea, data mining, manuscript draft, and analysis; E. Schlofmitz: study idea, data mining, critical review of the manuscript; G. D. Melaku, K. O. Kuku, and Y. Kahsay: data mining, critical review of the manuscript; R. Schlofmitz, and A. Jeremias: writing, critical review of the manuscript; H. M. Garcia-Garcia: study idea, data analysis, data mining, preparation, and critical review of the manuscript.

CONFLICTS OF INTEREST

H.M. Garcia-Garcia declared having received institutional grant support from Biotronik, Boston Scientific, Medtronic, Abbott, Neovasc, Shockwave, Phillips, and Corflow. The remaining authors declared no conflicts of interest.

WHAT IS KNOWN ABOUT THE TOPIC?

- Percutaneous coronary interventions rely on angiography to inform most of the clinical decisions on lesion preparation; however, the extent of calcium is poorly assessed on the angiography.
- The relation between the ICA and the OCT regarding the severity of CP was examined using thickness and angle measurements on the OCT.
- No examination has been conducted of all OCT measurements and their relation to the severity of CP as seen on the ICA.

WHAT DOES THIS STUDY ADD?

- Compared to the OCT, the ICA has a low sensitivity but a high specificity to detect severely calcified plaques.
- As calcium increased on the OCT measurements regarding area, length, thickness, and angle so did the number of angio-defined severe CP lesions, which is indicative that all OCT measurements can be used to detect severely calcified lesions.
- The OCT offers a feasible alternative to the angiography regarding calcium assessment; it extends calcium characterization by providing detailed information to shed light on the use of dedicated calcium debulking therapies for lesion preparation.

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Original article

5-year results of cutting or scoring balloon before drug-eluting balloon to treat in-stent restenosis

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ABSTRACT

Introduction and objectives: Drug-eluting balloon (DEB) angioplasty is an effective technique to treat in-stent restenosis (ISR). Neointimal modification with cutting balloon (CB) or scoring balloon (SB) enhances the angiographic results of DEB, but with no benefits have been reported in the clinical endpoints at the mid-term. There is lack of information on the clinical long-term results of this strategy. We aim to compare very long-term results of CB before DEB vs standard DEB to treat real-world patients with ISR.
Methods: Retrospective cohort registry of DEB PCIs to treat ISR defined by the use of CB. The primary endpoint was clinically driven target lesion revascularization (TLR) at 5 years. The secondary endpoints were based on the ARC-2 criteria.
Results: From January 2010 to December 2015, 107 ISRs were treated with DEB in 91 patients. CBs were used in 51 lesions (46 patients). Both cohorts were well balanced regarding clinical, lesion, and procedural characteristics. Compared to standard DEBs, CBs showed lower, although statistically non-significant rates, of TLR at 5 years (9.8% vs 23.6%, OR, 0.36; 95% confidence interval 0.19 to 1.09 P = .05). The Kaplan-Meier cumulative incidence of time until TLR showed similar results (log-rank test P value = .05) with similar rates of TLR at 1 year (3.9% vs 7.1%, P = .68) as curve separation in the long-term. There were no differences in the secondary endpoints. No stent thrombosis was reported.
Conclusions: In a real-world setting, neointimal modification with CB before DEB vs standard DEB to treat ISR shows lower, although statistically non-significant rates of TLR at 5 years. This benefit has been confirmed in the long-term and is consistent with bare-metal and drug-eluting stents.

Palabras clave: Balón farmacoactivo. Reestenosis. Balón de corte.

Resultado a los 5 años del balón de corte o incisión en el tratamiento de la reestenosis de stent coronario con balón farmacoactivo

RESUMEN

Introducción y objetivos: El uso de balón farmacoactivo (BFA) es una estrategia efectiva en el tratamiento de la reestenosis de *stents* coronarios (RIS). La modificación neointimal con balón de corte (BC) o incisión junto con BFA se asocia a mejores resultados angiográficos, aunque sin impacto en eventos clínicos a medio plazo. Los resultados clínicos de esta estrategia a muy largo plazo en la vida real son desconocidos. Se evaluó la eficacia de BC junto con BFA frente a BFA estándar en un registro de pacientes de la vida real con RIS a muy largo plazo (5 años).
Métodos: Registro retrospectivo de 2 cohortes de pacientes con RIS tratados con BFA, definidas por el uso de BC. El evento primario fue la tasa de revascularización clínicamente indicada de la lesión tratada a 5 años. Se valoraron eventos secundarios según los criterios ARC-2.
Resultados: Entre enero de 2010 y diciembre de 2015 se usó BFA en 107 RIS en 91 pacientes. En 51 lesiones (46 pacientes) se utilizó BC. Ambas cohortes presentaron similares características clínicas y de procedimiento. Respecto al uso estándar de BFA, el BC consiguió una reducción numérica, pero no significativa, en la tasa de revascularización de la lesión tratada a 5 años (9,8% frente a 23,6%; *odds ratio* = 0,36; intervalo de confianza del 95%, 0,19-1,09; p = 0,05). El análisis de incidencia acumulada de Kaplan-Meier mostró resultados parecidos (*log-rank*, p = 0,05), con similar tasa de eventos a 1 año (3,9% frente a 7,1%; p = 0,68), y separación de las curvas con el tiempo. No se evidenciaron diferencias en los eventos secundarios. No hubo trombosis de *stent* en la cohorte.
Conclusiones: En una cohorte de la vida real, la modificación neointimal de la RIS con BC junto con BFA, en comparación con BFA estándar, logra una reducción numérica, pero no significativa, en la tasa de revascularización de la lesión tratada a 5 años. El beneficio de esta estrategia se evidencia a largo plazo y es consistente entre RIS de *stent* convencional y de *stent* farmacoactivo.

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Keywords: Drug-eluting balloon. In-stent restenosis. Cutting/scoring balloon.

Abreviaturas

BC: balón de corte o incisión. **BFA:** balón farmacoactivo. **RIS:** reestenosis de *stent* coronario. **RLT:** revascularización de la lesión tratada. **SFA:** *stent* farmacoactivo. **SM:** *stent* convencional.

INTRODUCTION

In-stent restenosis (ISR) is a common problem in the routine clinical practice regarding percutaneous coronary intervention (PCI), and its management is associated with high rates of target lesion revascularization (TLR).[1] Together with the implantation of a new everolimus drug-eluting stent, the PCI with drug-coated balloon (DCB) is the strategy of choice to treat ISR after bare-metal stent (BMS) and drug-eluting stent (DES) implantation, and has a class I indication after confirmation that it can reduce the rate of TLR at the follow-up without having to implant a new layer of metal into the artery.[2-5] Despite of this, TLR is still high in the long-term (up to 20% at 3 years),[6-11] which is suggestive that new strategies may be needed to improve these results.

The cutting balloon (CB) consists of small blades or nitinol bands on its surface to optimize the predilatation of coronary lesions by performing controlled fractures of the atheromatous plaque. Compared to the plain old balloon angioplasty, its use for the management of ISR is associated with structural changes of the neointima and acute improvements of the lumen area,[12] although no angiographic or clinical benefit has been reported in the mid-term.[13,14]

The efficacy of the DCB depends on the transfer of drug from the surface of the balloon to the tissue where it exerts it antiproliferative effect.[15] Theoretically speaking, greater the neointimal disarrays are associated with more effective transfers and smaller issue thickness. As a matter of fact, preclinical studies have suggested a greater effect of DCB inhibiting neointimal growth.[16] This greater disarray and reduction of the neointima can be achieved using a CB before the DCB.

Although this hypothesis has not been confirmed in animal models in the short-term,[17] the strategy has shown better angiographic results in the mid-term (6 to 8 months) (significant reduction of binary restenosis), but no effect on TLR or clinical events at the 1-year follow-up.[18] No long-term results have been published on the use of this strategy.

Our objective was to assess the very long-term results of the use of CB plus DCB to treat ISR.

METHODS

Retrospective registry of cohorts of real-world patients with, at least, 1 ISR treated with DCB at a single high-volume PCI center (> 800/year) and a 5-year follow-up. Two different cohorts were defined based on the use of CB prior to the PCI with DCB (C_DCB) or standard DCB (S_DCB). The C_DCB cohort was defined by the use of, at least, 1 cutting balloon (Flextome Cutting Balloon, Boston Scientific, United States) or 1 scoring balloon (ScoreFlex, Orbus-Neich, China). The use of the CB was left to the operator's discretion. The ISR was defined as an angiographic stenosis > 50% in 2 different orthogonal radiographic projections inside the stent or < 5 mm from its borders plus symptoms of angina or objective confirmation of myocardial ischemia or fractional flow reserve/positive instantaneous wave-free ratio. Lesions were treated with 2 types of drug-coated balloons based on their availability at the time: the SeQuent Please (B. Braun Surgical, Germany) or the Pantera Lux (Biotronik, Switzerland). Data on the long-term progression of patients with ISR treater with the SeQuent Please DCB in this cohort regardless of the use of CB were reported beforehand.[19]

Exclusion criteria were cardiogenic shock or cardiac arrest in the index event, the presence of ≥ 3 layers of metal in the lesion with ISR and a contraindication to dual antiplatelet therapy with acetylsalicylic acid and a $P2Y_{12}$ inhibitor for, at least, a month.

The clinical and procedural characteristics were obtained from the center and the cath lab databases. The coronary study of the lesions was performed with the Xcelera system (Philips, The Netherlands) using the projection with the highest degree of stenosis. The Mehran classification of ISR was used to categorize the lesions.[20] The strategy of the procedure including the use and type of CB was left to the operator's criterion. DCB dilatation lasted for, at least, 60 seconds at nominal pressure. The PCI, management, and previous and later treatment of the patients was performed based on the routine clinical practice.

The study was conducted in observance of the criteria established at the Declaration of Helsinki and the International Council on Harmonization Good Clinical Practice guidelines (ICH-GCP). Also, it was authorized by Hospital Clínico Lozano Blesa (Zaragoza, Spain) management and ethics committee. No informed consents were needed given the retrospective nature of the study. A 5-year long follow-up period was arranged. Every follow-up was performed by checking the electronic database of the regional healthcare system where all the patient's clinical events were thoroughly detailed. Data were anonymized through internal numerical identification at the cath lab.

All events were defined in a standard way according to the ARC-2 consensus.[21] The primary endpoint was the need for TLR with a clinically indicated DCB at 5 years and estimated on the overall number of all target lesions. Clinically indicated TLR was defined as a new-onset ISR > 70% or > 50% of the target lesion in the presence of ischemic symptoms, a positive inducible ischemia on stress testing dependent on the vessel or fractional flow reserve values ≤ 0.80 or instantaneous wave-free ratio values ≤ 0.89.

Secondary endpoints were the presence or lack of target vessel revascularization, and target vessel myocardial infarction (according to the universal definition[22]), all-cause mortality, death due to cardiac causes (acute myocardial infarction, severe arrhythmia, heart failure, unwitnessed or unknown death) or cardiovascular death (cardiac or stroke induced or due to other cardiovascular processes), BARC type ≥ 3 bleeding, stroke (new neurologic deficit > 24 h duration) or a composite endpoint of target lesion failure (TLR + target vessel myocardial infarction + cardiovascular death), target vessel failure (target vessel revascularization + target vessel

myocardial infarction + cardiovascular death) or patient-oriented composite endpoint (any revascularization + acute myocardial infarction + stroke + overall death). These endpoints were estimated on the overall number of patients. Definitive or probable stent thrombosis was also defined based on the ARC-2 criteria and estimated on the overall number of lesions.

Data mining and analysis were performed using the SPSS 19.0. statistical software (IBM, United States). Quantitative variables were expressed as mean and standard deviation. Qualitative variables were expressed as relative percentage. The cumulative incidence of the endpoints at the follow-up was also estimated. The variables and the group endpoints studied were compared on a bivariate analysis using the chi-square test (or Fisher's exact test, when appropriate) or the Student *t* test regarding the quantitative variables. Cox regression analysis was performed to estimate the primary endpoint predictors (including the variables associated with *P* values < .1). Survival was analyzed using the Kaplan-Meier method to build the cumulative incidence curve of time to the primary endpoint based on the strategy of treatment used. *P* values < .05 were considered statistically significant.

RESULTS

A total of 107 ISRs were treated with DCBs in 95 procedures performed on 91 patients from January 2010 through December 2015 (in 4 patients the PCI with DCB was repeated at the follow-up, in 1 case using a different DCB on the same previously treated lesion). A total of 51 lesions (42 patients) were treated with a PCI plus CB + DCB (C_DCB), and 56 lesions (49 patients) with standard DCB (S_DCB). A total of 53 lesions were treated with the SeQuent Please device, and 54 with the Pantera Lux. The cutting balloon and the scoring balloon were used in 36 and 15 lesions, respectively.

The study cohorts were similar regarding the clinical characteristics (table 1), and the lesion and procedural characteristics (table 2). Some of the differences reported in the C_DCB group where that radial access was more common, and the size of the stent and minimum lumen diameter were greater, although with a similar percent diameter stenosis of the lesion before and the after the PCI. Patients had a high prevalence of cardiovascular risk factors including diabetes in 35% of the cases. A total of 47 new coronary angiographies were performed at the follow-up. In 29 of these the target lesion had good results. The rate of new coronary angiography was similar in both groups (44.6% vs 41.2% in the C_DCB group. *P* = .71). A total of 18 TLRs were performed at the follow-up (16.8%) of which 17 were treated with a PCI (16 stent-in-stent), and 1 with coronary artery bypass graft. The rate of TLR was numerically lower in the C_DCB group at 1 (3.9% vs 7.1%; *P* = .68) and 3 years (9.8% vs 17.9%; *P* = .23). Compared to the S_DCB strategy, the use of the C_DCB reduced the 5-year rate of TLR although not statistically significant (9.8% vs 23.2%; OR, 0.36; 95% confidence interval [95%CI], 0.19-1.09; *P* = .05). The Kaplan-Meier analysis of the cumulative incidence curve revealed the differences seen at the 5-year follow-up (log-rank test, *P* = .05) with a similar 1-year event rate and curve separation consistent with the passing of the follow-up period (figure 1).

The 5-year cumulative incidence of secondary endpoints is shown on table 3. The incidence rate of target vessel-related composite endpoints (target lesion failure and target vessel failure) was numerically lower in the C_DCB group although not statistically significant. No differences were found in the remaining secondary endpoints. The overall mortality rate at the follow-up was 31.8% (n = 19) being neoplasms the most common cause (n = 7). The incidence rates of stroke and patient-oriented composite endpoint were high (10.9% and 51.6%, respectively), which was consistent with an old cohort with high cardiovascular risk. No cases of definitive or probable stent thrombosis were seen at the follow-up.

Table 1. Baseline characteristic of the patients

	S_DCB	C_DCB	*P*
	N = 49 patients/ 56 lesions	N = 42 patients/ 51 lesions	
Age	68.9 ± 11.3	67.7 ± 10	.58
Male	85.7% (35)	83.3% (35)	.75
Arterial hypertension	26.8% (14)	23.8% (10)	.6
Dyslipidemia	46.9% (23)	28.6% (12)	.7
Smoking	61.2% (30)	57.1% (24)	.69
Diabetes	37.5% (21)	35.3% (18)	.81
AF in oral anticoagulants	22.4% (11)	19% (8)	.38
Previous myocardial infarction	55.1% (27)	50% (21)	.62
Previous coronary artery bypass graft	6.1% (3)	4.8% (2)	1
CKD (GFR < 60mL/min)	32.7% (16)	33.3% (14)	.94
LVEF (%)	54 ± 10	55 ± 9	.51

AF, atrial fibrillation; CKD, chronic kidney disease; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction.

A Kaplan-Meier subanalysis based on ISR after BMS or DES implantation showed that the C_DCB strategy consistently reduced the 5-year rate of TLR in half with both types of stent although not statistically significant (figure 2).

Aside from the C_DCB no association was found between the variables and the 5-year rate of TLR except for the location of ISR that was 100% in cases found in coronary artery bypass graft stents (3 cases) compared to 14.4% in cases found in the native coronary tree (*P* = .003). The 5-year rate of TLR was similar in diabetic patients (17.9% vs 16.2%; *P* = .81) in the ISR of DESs (17.2% vs 16.3%; *P* = .9) and in stents < 3 mm (12.9% vs 18.4%; *P* = .58) without any differences based on the type of DCB used (Sequent, 20.4% vs Pantera, 13.2%; *P* = .32). In the Cox regression analysis, the use of the C_DCB was not an independent predictor of TLR at 5 years being the ISR of a coronary artery bypass graft the only independent predictor (OR, 5.4; 95%CI, 1.5-19.8; *P* = .01).

DISCUSSION

As far as we know, the study presented here is the first one to confirm:

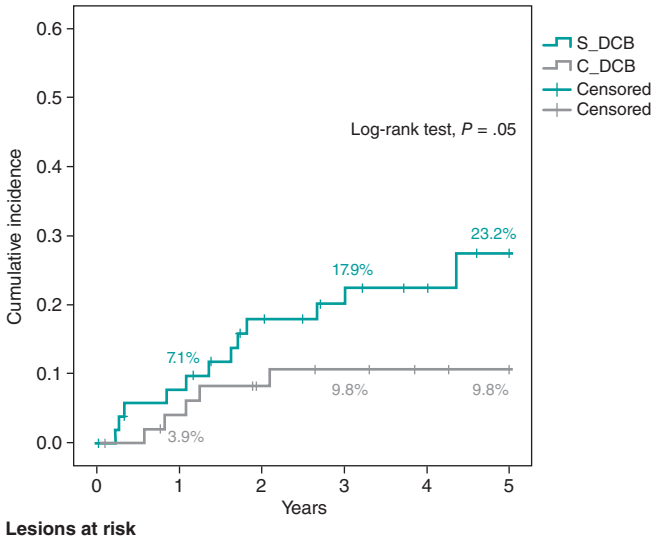
- The use of a CB in connection with a DCB in the ISR setting shows a tendency to reduce the rate of TLR.
- The benefit of this strategy is evident in the long-term.
- The benefit seems to be consistent in ISR after BMS and DES implantation.
- The strategy is safe and there are no traces of stent thrombosis when a CB is used.

Table 2. Lesion and procedural characteristics

	S_DCB	C_DCB	*P*
	N = 49 patients/ 56 lesions	N = 42 patients/ 51 lesions	
Procedural characteristics			
Clinical signs			.87
Stable angina	55.4% (31)	56.9% (29)	
Unstable angina/ NSTEACS	41.1% (23)	41.2% (21)	
STEACS	3.6% (2)	2% (1)	
Radial access	55.4% (31)	78.4% (40)	.01
DCB caliber (mm)	3.03 ± 0.37	3.15 ± 0.42	.13
DCB length (mm)	20.2 ± 5.8	19.5 ± 4.7	.53
DCB inflation pressure (atm)	14 ± 3	14 ± 3	.81
CB caliber (mm)	N/A	2.93 ± 0.45	
CB length (mm)	N/A	8 ± 3	
CB inflation pressure (atm)	N/A	14 ± 3	
NCB	53.6% (30)	70.6% (36)	.07
NCB caliber (mm)	3.12 ± 0.42	3.28 ± 0.43	.14
NCB length (mm)	13.2 ± 3.1	12.6 ± 3.8	.65
NCB inflation pressure (atm)	18 ± 4	18 ± 3	.74
Intracoronary imaging	8.9% (5)	5.9% (3)	.55
Multivessel disease	62.7% (32)	47.7% (21)	.14
Complete revascularization	82.4% (42)	93.2% (41)	.13
$P2Y_{12}$ inhibitor			.64
Clopidogrel	88.2% (45)	81.6% (36)	
Prasugrel	3.9% (2)	4.5% (2)	
Ticagrelor	7.8% (4)	13.6% (6)	
Duration of dual antiplatelet therapy			.27
1 month	3.9% (2)	2.3% (1)	
3 months	21.6% (11)	9.1% (4)	
6 months	21.6% (11)	34.1% (15)	
12 months	52.9% (27)	54.5% (24)	

	S_DCB	C_DCB	*P*
	N = 49 patients/ 56 lesions	N = 42 patients/ 51 lesions	
Lesion characteristics			
Location of ISR			.35
LAD	53.6% (30)	45.1% (23)	
LCX	23.2% (13)	15.7% (8)	
RCA	16.1% (9)	31.4% (16)	
LMCA	5.4% (3)	3.9% (2)	
Coronary artery bypass graft	1.8% (1)	3.9% (2)	
Mehran's angiographic classification of ISR pattern			.42
IA	1.8% (1)	3.9% (2)	
IB	3.6% (2)	0% (0)	
IC	41.1% (23)	49% (25)	
ID	1.8% (1)	3.9% (2)	
II	21.4% (12)	27.5% (14)	
III	21.4% (12)	11.8% (6)	
IV	8.9% (5)	3.9% (2)	
ISR based on type of stenting			.4
BMS	53.6% (30)	37.3% (19)	
DES	33.9% (19)	45.1% (23)	
DES in BMS	8.9% (5)	11.8% (6)	
DES in DES	3.6% (2)	5.9% (3)	
Time from implantation	4.1 ± 4.8	3.8 ± 5	.69
Bifurcation	32.1% (18)	23.5% (12)	.32
Stent caliber (mm)	2.96 ± 0.43	3.1 ± 0.56	.02
Stent length (mm)	22.4 ± 6.5	22.8 ± 7.1	.75
Reference diameter (mm)	2.98 ± 0.48	3.12 ± 0.53	.16
Minimum lumen diameter (mm)	0.73 ± 0.51	0.68 ± 0.5	.67
Length (mm)	13.2 ± 5.6	11.7 ± 5.3	.18
Stenosis (%)	72 ± 18	75 ± 16	.3
Minimum lumen diameter post-PCI (mm)	2.43 ± 0.46	2.77 ± 0.62	.002
Acute lumen gain (mm)	1.7 ± 0.64	2.08 ± 0.83	.01
Stenosis post-PCI (%)	14 ± 5	14 ± 6	.45
Final TIMI grade 3 flow	98.2% (55)	100% (51)	1

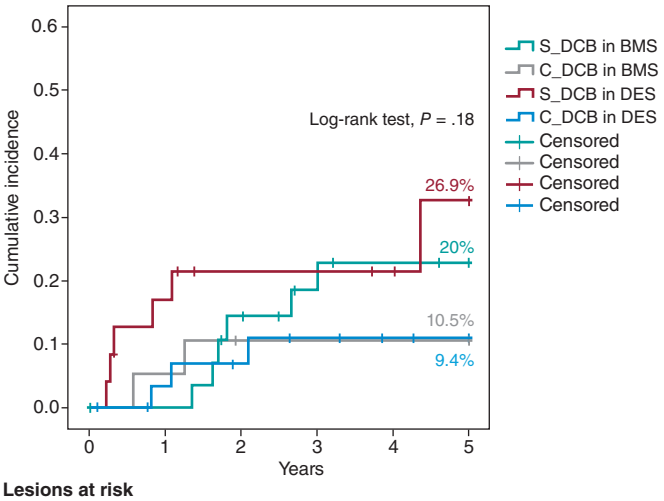
BMS, bare-metal stent; CB, cutting balloon; DCB, drug-coated balloon; DES, drug-eluting stent; ISR, in-stent restenosis; LAD, left anterior descending coronary artery; LCX, left circumflex artery; LMCA, left main coronary artery; NCB, non-compliant balloon; NSTEACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEACS, ST-segment elevation acute coronary syndrome; TIMI, Thrombolysis in Myocardial Infarction.



Lesions at risk

S_DCB	56	46	34	26
C_DCB	51	45	36	32

Figure 1. Kaplan-Meier analysis of the 5-year cumulative incidence of target lesion revascularization. DCB, drug-coated balloon.



Lesions at risk

S_DCB in BMS	30	27	19	15
C_DCB in BMS	19	18	16	15
S_DCB in DES	26	19	16	12
C_DCB in DES	32	28	21	17

Figure 2. Kaplan-Meier analysis of the 5-year cumulative incidence of target lesion revascularization based on whether the stent is made out of metal or is drug-eluting. BMS, bare-metal stent; DCB, drug-coated balloon, DES, drug-eluting stent.

Table 3. 5-year cumulative incidence of primary and secondary endpoints

	S_DCB	C_DCB	*P*
	N = 49 patients/ 56 lesions	N = 42 patients/ 51 lesions	
Primary endpoint			
TLR (clinically justified)	23.2% (13/56)	9.8% (5/51)	.05
Secondary endpoints			
Target vessel revascularization	28.6% (16/56)	17.6% (9/51)	.18
Any revascularization	28.6% (14/49)	26.2% (11/42)	.8
Target vessel myocardial infarction	7.1% (4/56)	5.9% (3/51)	.79
Myocardial infarction	18.3% (9/49)	7.2% (3/42)	.19
Death due to cardiac causes	4.1% (2/49)	4.8% (2/42)	1
Cardiovascular death	16.3% (8/49)	11.9% (5/42)	.54
Overall mortality	36.7% (18/49)	26.2% (11/42)	.28
Stroke	10.2% (5/49)	11.9% (5/42)	.55
BARC type 3-5 bleeding	7.1% (4/49)	3.9% (2/42)	.68
Target lesion failure	37.5% (21/56)	25.5% (13/51)	.18
Target vessel failure	41.1% (23/56)	25.5% (13/51)	.08
POCE	53.1% (26/49)	50% (21/42)	.77

BARC, Bleeding Academic Research Consortium; DCB, drug-coated balloon; POCE, patient-oriented composite endpoints; TLR, target lesion revascularization.

Compared to the plain old balloon angioplasty for the management of ISR, the CB achieves greater lumen areas because it breaks down the elastic and fibrotic continuity of the neointima by reducing its integrity and resistence.[12] However, this acute angiographic improvement is not associated with lower but high rates of TLR (18% to 29%) at the 1-year follow-up.[13,14] Similarly, in our series, the use of the CB is associated with a significant increase of minimum lumen diameter and acute gain after the procedure (table 2) despite the fact that the caliber of non-compliant balloons and DCBs was similar between both groups. Although stent diameter was slightly larger in the C_DCB group, the final percent stenosis did not change significantly between both groups; still, this may be an important piece of information in our results since the size of the vessel has been described as an independent predictor of new restenosis.[23]

The use of the DCB to treat ISR is something common after several meta-analyses revealed that, together with DES implantation with in-stent everolimus, this strategy is the most effective one to avoid new revascularizations.[2-4] Afterwards, in the RIBS IV (with DES) and RIBS V (with BMS) clinical trials Alfonso et al. proved the long-term superiority of DES implantation with in-stent everolimus.[8,9,24] However, the philosophy of not adding a new metal layer (or delay it through time) and questions associated with its long-term safety[10,11] have turned DCB implantation into a common practice to treat ISR. Added to the RIBS IV-V studies, other trials have reported on the long-term effectiveness of DCB (PEPCAD[7] with BMS, and PEPCAD-DES[6] and ISAR-DESIRE 3[10] with DES). Overall, in these 5 studies, a total of 94 TLRs were reported in 524 ISRs treated with DCB, which is a 3-year rate of TLR of 17.9%. These results are accurately reproduced in our S_DCB cohort with rates high enough to justify looking into ways to improve the efficacy of DCBs.

The efficacy of DCBs is based on a transfer of the drug to the neointima of ISR where it exerts its antiproliferative effect. The proper preparation of the lesion by reducing neointimal thickening and increasing the surface of contact with the balloon is the key to achieve successful DCB implantations.[15] Preclinical studies suggest that greater neointimal disarrays can increase the release and

retention of the drug into the tissue, thus increasing its effects.[16] Considering the greater acute lumen gain and controlled disarray that the CB provides, results can improve if used together with the DCB. This hypothesis was put to the test, but not proven, in a preclinical trial. The reason was that the use of the CB was not associated with a lower neointimal volume or acute lumen loss. Nonetheless, this assessment was made was very early (28 days).[17]

The synergistic effects of CB plus DCB were also confirmed by Scheller et al.[25] in the PATENT-C trial. They took a different angle and studied the addition of an antiproliferative drug (paclitaxel) to the scoring balloon that reduced the 1-year rate of TLR significantly (3% vs 32%; $P = .004$). This information is consistent with the 1-year rate of TLR of 3.9 seen in our C_DCB cohort. From a new and different angle too, while still observing the philosophy of not leaving any material behind in the long-term after the PCI, Alfonso et al. conducted the RIBS VI Scoring trial and analyzed the impact of a CB before bioresorbable scaffold implantation to treat ISR. However, the 1-year rate of TLR was not reduced (9.8 vs 11.1%).[26]

Two randomized clinical trials have assessed the effect of CB implantation before DCB implantation to treat ISR. Aoki et al.[27] found no angiographic differences at the 8-month follow-up in the ELEGANT trial. However, this was a comparative study vs a non-compliant balloon. Kufner et al.[18] specifically tested the effects of CB implantation in the ISAR-DESIRE 4 trial. The primary endpoint was an angiographic result that confirmed that this strategy effectively reduced binary ISR at the 6 to 8-month follow-up. However, no differences were seen when the clinical events or TLR were assessed at the 1-year follow-up (16.2% vs 21.8%; P = .26). Qualitatively speaking, these results are consistent with what our series described because, although long-term benefits were reported, the 1-year rate of TLR did not change between our groups. No long-term data have ever been published so our cohort cannot be compared to corroborate the benefits described. Quantitatively speaking, we saw differences in the 1-year rate of TLR, much lower in our study (3.9% vs 7.1%). Three may be the reasons for this. In the first place, the scheduled angiographic assessment of the ISAR-DESIRE 4 trial because if we look at the Kaplan-Meier analysis of the TLR, in this study more clinical events were reported at the 6 to 8-month follow-up (when the angiographic assessment occurred). This is suggestive of a TLR guided by angiographic criteria (the so-called oculodilatory reflex) and not clinically justified as it was the case in our series. Secondly, the exclusive use of the scoring balloon vs the predominant use of the CB in our series since the CB achieves greater neointimal disarray and larger residual lumen diameters, thus increasing the efficacy of the DCB. Thirdly, the exclusive management of ISR after DES implantation vs ISR after any other type of stent implantation (BMS or DES) of our series since different authors have proposed the lower efficacy of the DCB to treat ISR after DES implantation.[11,28] Based on this previous knowledge a subanalysis of the C_DCB strategy based on the type of stent used was conducted (figure 2). A consistent efficacy both in BMSs and DESs was seen with a similar 5-year rate of TLR in both subgroups (10.5% and 9.4% respectively)

Treating ISR with DCBs is a safe strategy associated with very low rates of stent thrombosis (around 1%) at the long-term follow-up.[11] The role that a greater CB-induced neointimal tissue disarray plays in the appearance of thrombotic phenomena on the lesion is unknown. Consistent with the mid-term results of theISAR-DESIRE 4 trial, in our series, long-term target lesion thrombosis is null, which is a guarantee that the use of C_DCB is safe.

Limitations

Our study has several limitations. It is a retrospective, observational, and single-center study. Although the use of the DCB is the treatment of choice for the management of ISR in our center, it is possible that patients with more unfavorable ISR may have been excluded for having been treated with a DES. The use of intracoronary imaging was limited and the characterization of ISR could have given relevant information on the therapeutic strategy used and its long-term results. The size of the sample was not big enough to obtain powerful evidence. A larger sample size and longer follow-up is, therefore, guaranteed.

CONCLUSIONS

In a real-world cohort, changing the neointima of ISR with CB plus DCB vs standard DCB reduces the 5-year rate of TLR although not statistically significant. The benefit of this strategy is evident in the long-term and consistent between ISR after BMS and DES implantation.

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AUTHORS' CONTRIBUTIONS

J.A. Linares Vicente: study design, data mining, and analysis and writing of the manuscript. J.R. Ruiz Arroyo: data and critical review of the manuscript. A. Lukic, B. Simó Sánchez, and O. Jiménez Meló: data mining. A. Riaño Ondiviela, P. Morlanes Gracia, and P. Revilla Martí: data mining.

CONFLICTS OF INTEREST

None reported.

WHAT IS KNOWN ABOUT THE TOPIC?

- The use of CB to treat ISR with DCB has been associated with better angiographic results although with no impact on the mid-term clinical events. The clinical outcomes of this long-term strategy are still unknown.

WHAT DOES THIS STUDY ADD?

- The use of CB plus DCB to treat ISR is associated with lower rates of TLR. The benefit of this strategy has been reported in the long-term. This benefit seems to be consistent with both ISR after BMS and DES implantation.

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Original article

Rationale and design of the Concordance study between FFR and iFR for the assessment of lesions in the left main coronary artery. The ILITRO-EPIC-07 Trial

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ABSTRACT

Introduction and objectives: Patients with left main coronary artery (LMCA) stenosis have been excluded from the trials that support the non-inferiority of the instantaneous wave-free ratio (iFR) compared to the fractional flow reserve (FFR) in the decision-making process of coronary revascularization. This study proposes to prospectively assess the concordance between the two indices in LMCA lesions and to validate the iFR cut-off value of 0.89 for clinical use.
Methods: National, prospective, and observational multicenter registry of 300 consecutive patients with intermediate lesions in the LMCA (angiographic stenosis, 25% to 60%. A pressure gudiewire study and determination of the RFF and the iFR will be performed: in the event of a negative concordant result (FFR > 0.80/iFR > 0.89), no treatment will be performed; in case of a positive concordant result (FFR ≤ 0.80/iFR ≤ 0.89), revascularization will be performed; In the event of a discordant result (FFR > 0.80/iFR ≤ 0.89 or FFR ≤ 0.80/iFR > 0.89), an intravascular echocardiography will be performed and revascularization will be delayed if the minimum lumen area is > 6 mm^2. The primary clinical endpoint will be a composite of cardiovascular death, LMCA lesion-related non-fatal infarction or need for revascularization of the LMCA lesion at 12 months.
Conclusions: Confirm that an iFR-guided decision-making process in patients with intermediate LMCA stenosis is clinically safe and would have a significant clinical impact. Also, justify its systematic use when prescribing treatment in these potentially high-risk patients.
Registered at ClinicalTrials.gov (Identifier: NCT03767621).

Keywords: iFR. FFR. Left main coronary artery.

Justificación y diseño del estudio Concordancia entre RFF e iFR en lesiones del tronco común. Estudio iLITRO-EPIC-07

RESUMEN

Introducción y objetivos: Los pacientes con estenosis en el tronco coronario izquierdo (TCI) han sido excluidos de los ensayos que apoyan la no inferioridad del cociente de presiones en el índice diastólico instantáneo sin ondas (iFR) respecto a la reserva fraccional de flujo (RFF) en la toma de decisiones sobre revascularización coronaria. El presente estudio propone valorar de manera prospectiva la concordancia entre los dos índices en lesiones del TCI y validar el valor de corte del iFR de 0,89 para su uso clínico.
Métodos: Registro multicéntrico nacional, prospectivo, observacional, con la inclusión de 300 pacientes consecutivos con lesiones intermedias (estenosis angiográfica 25-60%) en el TCI. Se realizará un estudio con guía de presión y determinación de RFF e iFR. En caso de resultado concordante negativo (RFF > 0,80 / iFR > 0,89), no se realizará tratamiento; en caso de resultado concordante positivo (RFF ≤ 0,80 / iFR ≤ 0,89), se realizará revascularización; en caso de resultado discordante (RFF > 0,80 / iFR ≤ 0,89 o RFF ≤ 0,80 / iFR > 0,89), se realizará estudio con ecocardiografía intravascular y se considerará diferir la revascularización si el área luminal mínima es > 6 mm^2. El criterio de valoración clínico primario será la incidencia del combinado de muerte cardiovascular, infarto no mortal relacionado con la lesión del TCI o necesidad de revascularización de la lesión del TCI a los 12 meses.
Conclusiones: La demostración de la seguridad clínica en la toma de decisiones del iFR en pacientes con lesiones intermedias en el TCI tendría un impacto clínico importante y justificaría su uso sistemático para la decisión del tratamiento en estos pacientes de potencial alto riesgo.
Registrado en ClinicalTrials.gov (identificador: NCT03767621).

Palabras clave: iFR. RFF. Tronco coronario izquierdo.

Abbreviations

MLA: minimum lumen area. **FFR:** fractional flow reserve. **iFR:** instantaneous wave-free ratio. **IVUS:** intravascular ultrasound. **LMCA:** left main coronary artery.

INTRODUCTION

Assessing functional severity of coronary stenoses at left main coronary artery (LMCA) level through coronary angiography has serious limitations.[1] To treat angiographically intermediate stenoses (25% to 60% diameter) the use of invasive (ultrasound or optical coherence tomography) or functional imaging modalities (determining fractional flow reserve [FFR] to indicate the need for revascularization) has been proposed.[2] Patients with LMCA stenosis have traditionally been excluded from randomized clinical trials that assessed the prognostic capabilities of the functional assessment of coronary stenoses through the use of FFR.[3-5] The use of FFR to assess LMCA stenoses is backed by a limited number of non-randomized clinical trials that confirmed that FFR values > 0.80 is associated with a low risk of events if no revascularization is performed in patients with intermediate LMCA stenoses.[6]

The instantaneous wave-free ratio (iFR) is a new, easier-to-use, and cost-effective invasive index to assess the coronary function compared to FFR since there is no need to induce maximum coronary hyperemia to estimate it.[7] Although a non-inferior prognostic value of iFR compared to the FFR has recently been confirmed in

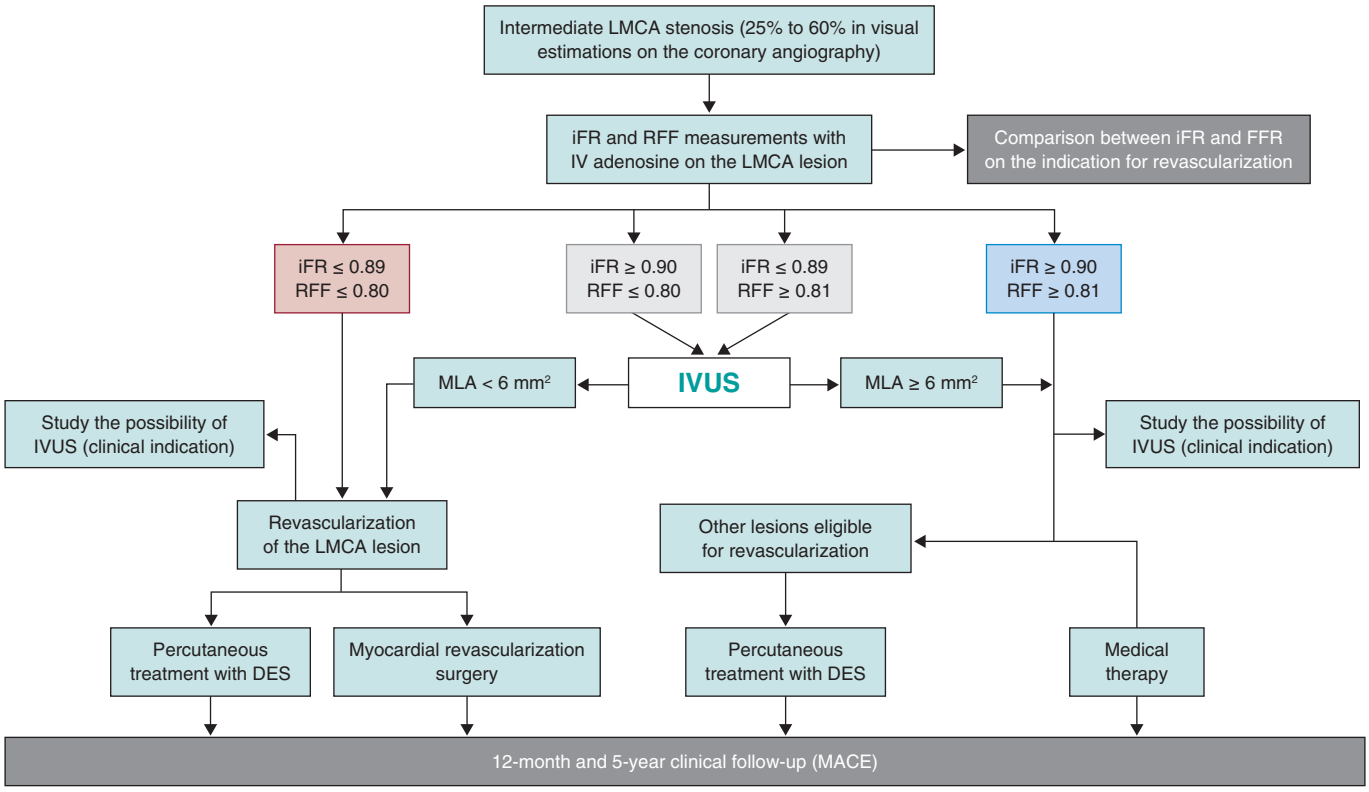

Figure 1. Decision-making algorithm based on the FFR and iFR results. DES, drug-eluting stent; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; IV, intravenous; IVUS, intravascular ultrasound; LMCA, left main coronary artery; MACE, major adverse cardiovascular events, MLA, minimum lumen area.

patients with intermediate lesions in 2 large trials, the presence of LMCA lesions was largely anecdotal or inexistent in both indices.[8,9] However, a non-randomized clinical trial has been published with a similar design to those previously conducted with the FFR that provides encouraging data on the value of iFR in the decision-making process regarding the LMCA. However, in such trial, the FFR—the most widely used index to assess intermediate LMCA stenoses—was not determined at the same time, which means that the results of this registry cannot be put into context.[10] Also, there are signs that the location of the LMCA lesion is a predictor of worse concordance between both indices.[11]

Proving the clinical safety of iFR in patients with intermediate LMCA lesions would have a major clinical impact and justify its systematic use in the decision-making process regarding the management of these high-risk patients.

The objective of this study is to assess the concordance between 2 physiological indices—the FFR and the iFR—in the assessment of intermediate LMCA lesions. Also, to validate prospectively the clinical safety profile of a revascularization strategy based on an iFR cut-off value of 0.89.

METHODS

Study design

National, prospective, observational, and multicenter registry including 300 consecutive patients with intermediate LMCA lesions (25% to 60% angiographic stenosis). A study will be conducted in all patients using intracoronary guidewire pressures. Also, both the FFR and the iFR values will be determined distal to the LMCA. Per protocol it is advised that the indication for revascularization should be decided based on the result of the iFR in such a way that:

- In patients with iFR and FFR values in the LMCA lesion > 0.89 and > 0.80, respectively clinical follow-up without LMCA lesion revascularization is indicated. In the presence of other lesions outside the LMCA with percutaneous revascularization criteria, the revascularization of these other lesions is indicated.

- In patients with iFR and FFR values in the LMCA lesion ≤ 0.89 and ≤ 0.80, respectively the revascularization of the LMCA lesion is indicated (percutaneous through a drug-eluting stent or surgical). In the presence of other lesions outside the LMCA with revascularization criteria (whether percutaneous or surgical), the revascularization of these other lesions is indicated.

- In case of discrepancy between the FFR and the iFR (positive vs negative or vice versa with 2 or more points above or below the respective cut-off value) an intravascular ultrasound (IVUS) should be performed to decide whether to indicate revascularization or not; with minimum lumen areas (MLA) > 6 mm² revascularization is ill-advised.

Patients whose management is not consistent with what the iFR value recommends will not be addressed for the strategy safety analysis, and clinical outcomes will be assessed separately.

Figure 1 shows the decision-making algorithm based on FFR and iFR results. IVUS is indicated in controversial cases, and recommended in the remaining cases to determine the correlation between the MLA and the iFR.

Table 1. Inclusion and exclusion criteria of the iLITRO-EPIC-07 trial

Inclusion criteria
Patients with intermediate LMCA lesions (25% to 60% angiographic stenosis on visual estimations) eligible for a pressure guidewire study to determine the iFR
Patients aged ≥ 18 years
Patients capable of giving their informed consent
Exclusion criteria
Patients with an indication for coronary artery bypass graft regardless of the significance of the LMCA lesion
Patients with LMCA lesions showing ulceration, dissection or thrombus
Patients with lesions in a previously non-dysfunctional arterial or venous graft in the territory irrigated by the LMCA (protected LMCA)
Patients with acute coronary syndrome with potentially culprit lesion in the LMCA
Patients incapable of giving their informed consent

iFR, instantaneous wave-free ratio; LMCA, left main coronary artery.

In patients eligible for percutaneous treatment, IVUS is highly recommended, and its utility will be assessed prospectively during the planning and optimization of the procedure.

Clinical follow-up is advised from 12 months to 5 years to determine the prognostic primary endpoint by assessing a composite endpoint of cardiovascular death, LMCA lesion-related non-fatal infarction or need for LMCA revascularization at the 12-months and 5-year follow-up.

Notifications

The study has been approved by the reference ethics committee and notified to the local ethics committee of all participant centers. The study has been registered in Clinicaltrials.gov with registration number NCT03767621. Devices with CE marking have only been used, and only for the indications already approved. The study observes the principles established by the Declaration of Helsinki. All patients gave their prior written informed consent to participate in the study.

Study population

Patients with suspected or confirmed ischemic heart disease on whom a coronary angiography is performed that detects intermediate angiographic LMCA stenoses (between 25% and 60%). Also, patients in whom intracoronary pressure guidewires are used to determine the iFR and the FFR in the LMCA lesion to decide on the indication for myocardial revascularization—whether percutaneous with a DES or surgical—based on the indication considered more appropriate.

Inclusion and exclusion criteria are shown on table 1. In cases of severe lesions at left anterior descending coronary artery or left circumflex artery level, the patient will not be included in the study unless the LMCA lesion is assessed after the percutaneous treatment of these lesions while taking into account that, if the LMCA lesion is significant, treatment will be percutaneous.

Table 2. Secondary endpoints of the iLITRO-EPIC-07 trial

Correlation between the assessment obtained through pressure guidewire (iFR) and the minimum lumen area measured through IVUS
Role of IVUS in the planning of treatment in the subgroup of patients treated with percutaneous therapy
Role of IVUS in the optimization of treatment in the subgroup of patients treated with percutaneous therapy
All-cause mortality at 12 months and 5 years
Cardiovascular death at 12 months and 5 years
Non-fatal infarction at 12 months and 5 years
LMCA lesion-related non-fatal infarction at 12 months and 5 years
Revascularization at 12 months and 5 years
Myocardial infarction associated with the revascularization of the LMCA (whether percutaneous or surgical)
Thrombosis of 1 or several stents in the LMCA at 12 months and 5 years
Restenosis of 1 or several stents in the LMCA at 12 months and 5 years
New target lesion revascularization in the LMCA (whether percutaneous or surgical) at 12 months and 5 years

iFR, instantaneous wave-free ratio; LMCA, left main coronary artery; IVUS: intravascular ultrasound.

Study endpoints

The iLITRO-EPIC 07 trial has 2 primary endpoints:

1) To establish concordance before indicating revascularization between 2 invasive functional assessment indices through intracoronary pressure guidewire in intermediate LMCA lesions with FFR and iFR cut-off values ≥ 0.80 (with IV adenosine) and ≥ 0.89 to delay treatment.

2) To validate prospectively the safety profile associated with the decision-making process regarding the revascularization of intermediate LMCA stenoses based on an iFR cut-off value of 0.89 measured using an intracoronary pressure guidewire to decide whether to revascularize or not based on the number of patients with delayed LMCA revascularization of the composite endpoint of cardiovascular death, LMCA lesion-related non-fatal infarction or need for LMCA revascularization at the 12-month follow-up.

Secondary endpoints are to determine the correlation between the iFR value in these lesions and the MLA determined by the IVUS and the utility of IVUS for the planning and optimization of LMCA lesions (table 2).

Study procedure

Figure 2 shows the procedure methodology on a flowchart.

Protocol to perform a study using a pressure guidewire

The patient is eligible for functional assessment in the presence of intermediate LMCA stenoses with visual estimations on the coronary angiography between 25% and 60%.

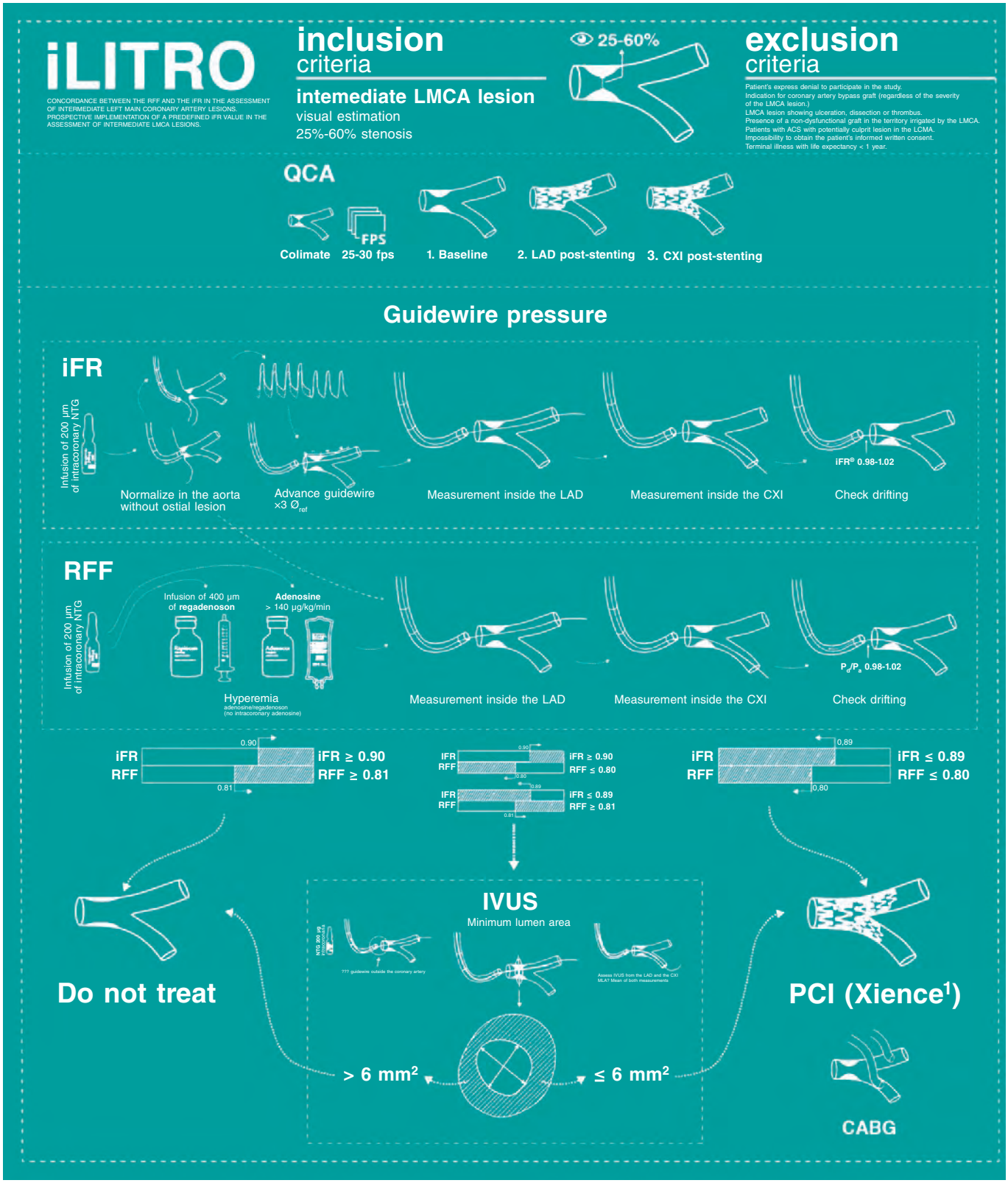

Figure 2. Study protocol and procedures. ACS, acute coronary syndrome; CABG, coronary artery bypass graft; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; LCX, left circumflex artery; LMCA, left main coronary artery; MLA, minimum lumen area; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography.

After catheterization using a guide catheter, at least, 200 µg of intracoronary nitroglycerin should be administered to keep coronary reactivity under control. Afterwards, the intracoronary guidewire should be advanced with the sensor placed in the ostium of the guide catheter; also, pressure curves should be brought back to normal for 5 to 10 heart beats. if the lesion has an ostial location, normalization will occur by removing the guide catheter from the coronary artery and placing the guidewire into the aorta. Afterwards, the guidewire should be removed from the catheter, and coronary catheterization performed to advance the guidewire.

The pressure guidewire should be advanced until, at least, 3 times the diameter of the vessel beyond the most distal stenosis to be able to measure the iFR according to the standard protocol.

After measuring the iFR, the guidewire should be removed with pressure curve monitorization until the inside of the guide catheter. At this point, the presence of the pressure calibration loss phenomenon (drifting) should be discarded. In case of overt drift (Pd/Pa measured on the catheter tip < 0.98 or > 1.02) measures should be taken again.

Afterwards, the FFR will be determined during hyperemia through the administration of adenosine in continuous IV infusion at doses ≥ 140 µg/kg/min for, at least, 2 minutes or an IV bolus of 0.4 mg of regadenoson.

After measuring the FFR, the guidewire should be removed with pressure curve monitorization until the inside of the guide catheter. At this point, the presence of drifting should be discarded. In case of overt drift (Pd/Pa measured on the catheter tip < 0.98 or > 1.02) measures should be taken again.

In case of discrepancy between the results of the FFR and the iFR (FFR ≤ 0.80 with iFR ≥ 0.90 or FFR ≥ 0.81 with iFR ≤ 0.89) IVUS will be performed, and the MLA determined. Revascularization will be indicated with MLAs < 6 mm^2 based on the results from the LITRO trial.[12]

Protocol to conduct IVUS studies

IVUS studies will be mandatory if the FFR and the iFR disagree. In patients eligible for percutaneous treatment of their LMCA lesions, the IVUS is highly recommended to guide the procedure. In the remaining patients (when iFR-guided medical therapy or surgical revascularization is decided) the IVUS is recommended to establish the correlation between the iFR value and the MLA measured on the LMCA whenever possible. The IVUS system used can be mechanical or rotational with resolutions between 20 MHz and 60 MHz.

An 0.014 in intracoronary guidewire will be advanced to perform the IVUS study (it can be the same pressure guidewire used to determine the iFR) towards the left anterior descending or left circumflex coronary arteries. After the administration of 200 µg of intracoronary nitroglycerin, the IVUS catheter will be advanced distal to the LMCA bifurcation. Afterwards, the catheter will be manual or automatically removed until the ascending aorta. It is essential that the guide catheter should remain outside the coronary artery to study the left main coronary artery entirely including its ostial region. The catheter will be placed in the left anterior descending coronary artery (preferably) or left circumflex artery or both (to conduct 2 studies with MLA determination from these positions and eventually pick the one with the lowest values).

In cases of catheter backward jump, even on manual mode (with calcified angulation) it is recommended to move the catheter forward from the aorta to acquire images of the region of interest that had not been properly assessed.

Technical aspects of the assessment of left main coronary artery lesions through fractional flow reserve

The study of LMCA lesions using pressure guidewires has some particularities that should be addressed when conducting the study.

Location of the lesion

A total of 3 different possible lesion locations can be anatomically distinguished on the LMCA depending on whether there is damage to the ostium, body or distal portion (bifurcation). The location of the lesion inside the LMCA has implications when conducting the study with the pressure guidewire. When the lesion is found in the ostium or the body, catheterization should be coaxial. Non-coaxial catheterization involves contact of the catheter lumen with the vessel wall to the extent that it can dampen the aortic pressure and artificially elevate the value of the FFR. For this reason, non-selective catheterization is advised when equalizing or normalizing the catheter and guidewire pressures when the latter is placed distal to the lesion to measure the FFR during maximum hyperemia. When the lesion is found in the LMCA distal portion and there is damage to its origin and main branches, both the distal LMCA and each one of its branches should be treated as 1 functional unit regardless of the degree of damage to these branches. To estimate the FFR, measurements are taken from the left anterior descending and left circumflex coronary arteries. The LMCA lesion is considered functionally significantly when the measurements of either one of the 2 main vessels is < 0.80.

Induction of hyperemia

In the assessment of LMCA lesions the use of an intracoronary bolus of adenosine is ill-advised because, since the non-selective catheterization of the left coronary artery is required, part of the drugs administered never reach this coronary artery, which is why the induction of hyperemia can be suboptimal. For this reason, the IV administration of drugs whether adenosine (infusions of 140 µg/kg/min for, at least, 2 minutes) or regadenoson (doses of 0.4 mg in IV bolus) is advised.[13]

Presence of left anterior descending or left circumflex coronary artery lesions

The presence of 1 isolated LMCA lesion is not rare. A series of all-comers treated with diagnostic coronary angiography proved that, in patients with damage to the LMCA, only 9% had 1 single LMCA lesion, 17% had 1 LMCA lesion plus damage to 1 vessel, 35% had 1 LMCA lesion plus damage to 2 vessels, and 38% had LMCA disease plus damage to 3 vessels.[14]

Statistical analysis

Demographic, clinical, hemodynamic, and procedural data will be presented for the entire group. Continuous variables will be expressed as mean, and standard deviation (or if the distribution of the values do not follow a normal, as median, and interquartile range). Categorical variables will be expressed as frequencies and percentages. The data obtained will be studied using the unilateral analysis of variance (ANOVA) for the continuous variables, and Fisher's exact test or the chi-square test for the categorical variables, when appropriate. When appropriate, non-parametric tests

will be used with variables without a normal distribution or when normalization is not possible. The Kaplan-Meier survival curves will be presented for the previously specified criteria. The concordance analyses will be conducted using Cohen's kappa coefficient. Also, sensitivity, specificity, positive and negative predictive values, and the area under the receiver operating characteristic (ROC) curve will be estimated.

Data curation and monitorization

Clinical, angiographic, physiological, and IVUS data will all be saved in a safe electronic CRD managed by Fundación EPIC, the promotor of the study. Clinical data at both the 12-month and 5-year follow-up, as well as the presence of cardiovascular events at the follow-up will also be saved in the same electronic CRD.

DISCUSSION

The iLITRO-EPIC 07 trial has a double primary endpoint: on the one hand, to establish the concordance between 2 intracoronary physiological indices, the FFR and the iFR, when assessing the severity of intermediate LMCA lesions; on the other hand, to study the use of a predetermined iFR value to indicate the revascularization of intermediate LMCA lesions with an up to 5-year clinical follow-up.

Left main coronary artery disease. Implications for the interventional cardiologist

Significant LMCA disease, understood as a stenosis in its greater diameter > 50%, is associated with a poor mid-term prognosis. Studies prior to coronary revascularization confirmed survival rates < 40% at the 4-year follow-up after diagnosis.[15]

The limitations of the angiographic assessment of the severity of LMCA lesions are well established.[16-18] Before suggesting revascularization in a patient with LMCA lesions, in particular ostial lesions, it is important to know whether the lesion really needs to be revascularized, that is, whether it is hemodynamically significant. LMCA stenoses are found in between 4% to 9% of all diagnostic coronary angiographies.[1] Due to their anatomical location, catheter-induced artifacts or to the severity of distal lesions, among other factors, interpreting LMCA lesions is associated with the highest intra- and inter-observer variability compared to lesions found in other parts of the coronary tree.[16] When stenoses ≥ 50% were found in the CASS registry,[19] a second observer confirmed that the stenosis was not significant in 19% of the cases.

Several former studies have confirmed that the prognosis of patients with functionally insignificant LMCA lesions is favorable.[6] Also, that the surgical revascularization of hemodynamically insignificant lesions is associated with a high rate of early graft failure.[20]

The LITRO trial, led by the Spanish Society of Cardiology Working Group on Intracoronary Diagnostic Techniques, was a multicenter and prospective study. It proved that, in patients with angiographically intermediate LMCA lesions, the presence of a MLA ≥ 6 mm^2 measured on the IVUS allows us to delay revascularization in a safely manner.[12]

Evidence to guide the revascularization of the left main coronary artery through functional assessment

To this date, no definitive data on the prognostic value of iFR measurements in intermediate LMCA stenoses have been published. The presence of a significant stenosis (> 70%) on the coronary angiography was an exclusion criteria in the DEFER, FAME, and FAME II clinical trials, as well as in the DEFINE FLAIR trial. Only the IFR SWEDEHEART trial included 30 patients with significant LMCA stenoses (1.6% of all the patients included).[3-5,8,9] An observational and retrospective study of 314 patients confirmed that delaying the revascularization of the LMCA using a iFR cut-off value of 0.89 as the guide was safe at the 30-month clinical follow-up.[10] However, in this observational registry the FFR, a widely validated index in the LMCA, was not obtained at the same time. This means that the results reported by this registry cannot be put into context and the concordance between both indices cannot be analyzed either.

The data available that support the use of the FFR in LMCA lesions come from several studies shown on table 1. The cut-off values used in these studies go from 0.75 to 0.80. In the study that has included, to this date, the highest number of patients with intermediate angiographic lesions, 213, only patients with FFR values < 0.80 were treated. However, in patients with higher values a conservative manage was used. No differences in the mortality or severe cardiovascular event rates were reported at the 5-year follow-up.[6] Therefore, the reference FFR value for LMCA lesions, as well as the remaining lesions, is < 0.80.

A metanalysis that included data from 8 landmark studies found no differences in the primary endpoint of death, non-fatal myocardial infarction or revascularization. However, the need for revascularization was greater in the group on medical therapy: whether this was primarily due to the revascularization of the LMCA is still under discussion.[21]

A recent study that assessed the correlation between the FFR and the iFR values based on the location of the lesion studied revealed that such correlation was weaker when the lesion was found on the LMCA or in the proximal left anterior descending coronary artery compared to other locations. This was attributed to a greater amount of vessel-dependent myocardium in these proximal lesions. Taking the FFR value and an iFR cut-off value ≥ 0.89 as a reference, both the false positives (21.9%) and the false negatives (26.7%) were more evident when the lesion was found on the LMCA or the proximal left anterior descending coronary atery.[11] Some studies have suggested that resting indices like the iFR could provide better measurements of coronary flow during hyperemia compared to the FFR.[22,23] This means that using the FFR as the gold standard could be questionable in this setting. Also, the scientific evidence available indicates that the discrepancies seen between the iFR and the FFR are not associated with a worse prognosis.[24] This means that the present study could clarify whether the iFR is associated with a weaker indication for revascularization in intermediate LMCA lesions with the exact same clinical safety compared to the FFR.

CONCLUSIONS

The iLITRO-EPIC 07 trial is the first prospective study to assess the concordance between the FFR and the iFR in intermediate LMCA lesions. Also, that it is safe to guide the indication for revascularization based on an iFR cut-off value of 0.89.

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the development of the study whatsoever including recruitment, follow-up, data curation, result analysis and interpretation, writing or final approval of both the protocol and this manuscript. The authors are solely responsible for the study design, writing, edition, and final version of the manuscript.

AUTHORS' CONTRIBUTIONS

All the authors are lead investigators of the iLITRO-EPIC07 trial at their corresponding working centers, collaborated in the writing of the study protocol, and in the recruitment of the patients. The manuscript was written by O. Rodríguez-Leor, J.M. de la Torre-Hernández, and A. Pérez de Prado; the remaining authors reviewed the manuscript.

CONFLICTS OF INTEREST

A. Pérez de Prado declared to have received fees from iVascular, Boston Scientific, Terumo, B. Braun, and Abbott Vascular. José M. de la Torre Hernández is the editor-in-chief of *REC: Interventional Cardiology*. F. Alfonso, and J. Sanchis are associate editors of *REC: Interventional Cardiology*; the journal's editorial procedure to ensure impartial handling of the manuscript has been followed.

WHAT IS KNOWN ABOUT THE TOPIC?

- In intermediate LMCA stenoses (25% to 60% diameter) the use of invasive (ultrasound or optical coherence tomography) or functional imaging modalities (by measuring the FFR) has been proposed to eventually indicate the need for revascularization. Patients with LMCA stenoses were excluded from randomized clinical trials that assessed the prognostic capabilities of the functional assessment using the FFR.[3] However, its use has been backed by several non-randomized clinical trials that confirmed that values > 0.80 are indicative of a low risk of events if revascularization is eventually spared. The iFR is a new physiological index that does not require hyperemia to be determined, which simplifies the whole process. There are still no data on the concordance between both indices in LMCA lesions or the safety of this new index in the assessment of these patients.

WHAT DOES THIS STUDY ADD?

- The iLITRO-EPIC07 trial is an attempt to prospectively assess the concordance between the FFR and the iFR, as well as the safety profile of an iFR-guided revascularization strategy.

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Original article

Clinical follow-up of long nontapered sirolimus-eluting coronary stent in real-world patients with de novo lesions. The Billar registry

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ABSTRACT

Introduction and objectives: Coronary lesions with stent overlapping are associated with higher neointimal proliferation that leads to more restenosis. Furthermore, the tapering of coronary arteries is a major challenge when treating long coronary lesions. This study attempted to assess the safety and clinical level of performance of long nontapered sirolimus-eluting coronary stent systems (> 36 mm) to treat long and diffused de novo coronary lesions in real-world scenarios.
Methods: This was a prospective, non-randomized, multicentre study that included 696 consecutive patients treated with the long nontapered BioMime sirolimus-eluting coronary stent system in long and diffused de novo coronary lesions. The safety endpoint was major adverse cardiovascular events defined as a composite of cardiac death, myocardial infarction, clinically driven target lesion revascularization, stent thrombosis, and major bleeding at the 12-month follow-up.
Results: Of a total of 696 patients, 38.79% were diabetic. The mean age of all the patients was 64.6 ± 14 years, and 80% were males. The indication for revascularization was acute coronary syndrome in 63.1%. A total of 899 lesions were identified out of which 742 were successfully treated with long BioMime stents (37 mm, 40 mm, 44 mm, and 48 mm). The cumulative incidence of major adverse cardiovascular events was 8.1% at the 12-month follow-up including cardiac death (2.09%), myocardial infarction (1.34%), and total stent thrombosis (0.5%).
Conclusions: This study confirms the safety and good performance of long nontapered BioMime coronary stents to treat de novo coronary stenosis. Therefore, it can be considered a safe and effective treatment for long and diffused de novo coronary lesions in the routine clinical practice.

Keywords: Coronary angioplasty. Drug-eluting stent. Nontapered stents.

Seguimiento clínico del *stent* coronario largo no cónico de sirolimus en el mundo real en lesiones de novo. Registro Billar

RESUMEN

Introducción y objetivos: Las lesiones coronarias largas y difusas, cuando se tratan percutáneamente, requieren a menudo superposición de los *stents*, que se asocia a una mayor tasa de reestenosis. Por otro lado, el adelgazamiento progresivo de las arterias dificulta el tratamiento de las lesiones largas. En este estudio se analizan la seguridad y la eficacia clínica de los *stents* liberadores de sirolimus largos no cónicos (> 36 mm) para el tratamiento de lesiones largas *de novo* en un escenario real.

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Métodos: Estudio prospectivo, no aleatorizado, multicéntrico, con 696 pacientes consecutivos con implantación de *stent* BioMime largo no cónico para el tratamiento de lesiones coronarias *de novo* largas y difusas. El criterio de valoración de seguridad fueron los eventos adversos cardiovasculares mayores en el seguimiento, definidos como la combinación de muerte cardiaca, infarto de miocardio, necesidad de nueva revascularización en la misma lesión guiada por la clínica, trombosis del *stent* o hemorragia mayor a los 12 meses.
Resultados: De los 696 pacientes incluidos, el 38,79% eran diabéticos. La edad media fue de 64,6 ± 14 años y el 80% eran varones. La indicación de revascularización fue un síndrome coronario agudo en el 63,1%. Se identificaron 899 lesiones, de las que 742 se trataron con éxito con *stents* BioMime (37-40-44-48 mm). La incidencia acumulada de eventos adversos cardiovasculares mayores fue del 8,1% a los 12 meses, con un 2,09% de muertes de causa cardiaca, un 1,34% de infartos de miocardio y un 0,5% de trombosis del *stent*.
Conclusiones: El presente estudio confirma la seguridad y el buen perfil clínico a 12 meses del *stent* BioMime largo no cónico para el tratamiento de lesiones coronarias *de novo* largas y difusas, por lo que debe considerarse un tratamiento seguro y eficaz para este tipo de lesiones en la práctica clínica habitual.

Palabras clave: Angioplastia coronaria. *Stents* farmacoactivos. *Stents* largos no cónicos.

Abbreviations

CAD: coronary artery disease. **DES**: drug-eluting stent. **MACE:** major adverse cardiovascular events. **PCI:** percutaneous coronary intervention. **SES:** sirolimus-eluting stent. **ST:** stent thrombosis.

INTRODUCTION

The most widely used strategy to treat coronary artery disease (CAD) is percutaneous coronary intervention (PCI) with stent implantation, particularly with the current generation of drug-eluting coronary stents (DES), since their distinctive features improve the clinical outcomes of PCI.[1] However, the treatment of long and diffused coronary lesions remains challenging, especially in long lesions in tapered coronary arteries where variations in vessel diameter may require the implantation of > 1 stent per lesion.[2,3]

The use of either multiple stents or a single long stent are the most common treatment strategies for long and diffused lesions in tapered arteries. Both approaches may be associated with clinical failure due to the potential risk of mechanical mismatch of the stent size.[1,4,5] Multiple short overlapping stents with variable diameters are often implanted to adequately match the size of long tapered lesions. Because of potential discrepancies regarding diameters when using long nontapered stents, a proximal optimization technique may be used to reconstruct the vessel natural geometry. However, this solution does not come without problems such as stent fracture due to vessel rigidity, restenosis due to a higher vascular injury, delayed healing, very late stent thrombosis (ST), vessel aneurysm, side branch jailing, higher treatment cost, overuse of antirestenotic drugs, and increased exposure to radiation and contrast media, and death or myocardial infarction.[6,7]

A single long BioMime (Meril Life Sciences Pvt. Ltd., India), an ultrathin biodegradable polymer coated sirolimus-eluting coronary stent (SES) system, is often enough to treat long and diffused lesions. Thus, the local arterial walls can be saved from overexposure to drug/metal avoiding any potential associated adverse events at the follow-up like delayed healing, perioperative myocardial infarction (MI), risk of target lesion revascularization, and very late ST. The aim of this study was to evaluate the safety and level of performance of the long nontapered BioMime SES system (37 mm, 40 mm, 44 mm, 48 mm) in consecutive real-world patients with long and diffused de novo coronary lesions.

METHODS

Study design and population

This was a prospective, non-randomized, multicentre study that included a total of 696 consecutive patients (aged ≥ 18 years) from 14 clinical centers across Spain. All the study investigators are listed in the appendix of this article.

All consecutive patients included had been treated of long and diffuse de novo coronary lesions through the implantation of, at least, 1 long nontapered BioMime system (37 mm, 40 mm, 44 mm, 48 mm). The study was conducted in observance of the privacy policy of each research center including its rules and regulations for the appropriate use of data in patient-oriented research. This study was also conducted in observance of the Declaration of Helsinki, and approved by the ethics committee. Written informed consents were obtained from all the participants before the procedure.

Study device and procedure

The BioMime is a biodegradable polymer coated SES system with different lengths available to treat long and diffused coronary lesions. It uses an ultra-thin strut (65 µm), and a cobalt-chromium platform that has a unique hybrid design of open and closed cells with uniformly thin coating (2 µm) of bioabsorbable polymers, PLLA (poly-L-lactic acid), and PLGA (poly-lactic-co-glycolic acid). The stent elutes sirolimus (1.25 µg/mm^2) between 30 and 40 days after implantation. The currently available long lengths of BioMime are 37 mm, 40 mm, 44 mm, and 48 mm. The device is CE marked.

The PCI was performed according to the standard treatment guidelines and followed by each participant center. Predilatation and postdilatation were left to the operator's discretion though postdilatation was recommended per protocol.

Preoperatively, a 300 mg loading dose of aspirin plus a second anti-platelet agent (clopidogrel, ticagrelor, or prasugrel according to the clinical settings and operator's preference) were administered in all the consecutive patients included.

Postoperatively, all patients were administered a 12-month course of dual antiplatelet therapy plus aspirin (75 mg to 100 mg once a day) indefinitely beyond the first year. A 1.6- and 12-month clinical follow-up was conducted after the index procedure, as required, and based on symptoms.

Endpoints and definitions

The safety endpoints were the occurrence of major adverse cardiovascular events (MACE) at the 1-, 6-, and 12-month follow-up after the index procedure. MACE was defined as a composite of cardiac death, target vessel myocardial infarction, clinically driven target lesion revascularization, ST, and major bleeding.

MI was defined as the development of new pathological Q waves on the electrocardiogram or elevated creatinine kinase (CK) levels ≥ 2 times the upper limit of normal with elevated CK-MB levels in the absence of new pathological Q waves or new ischemic symptoms (eg, chest pain or shortness of breath).[8] Cardiac death was defined as any deaths resulting from AMI, sudden cardiac death, heart failure mortality or stroke. Clinically driven target lesion revascularization was defined as a new PCI performed on the target lesion or coronary artery bypass graft of the lesion in the previously treated segment or within the 5 mm proximal or distal to the stent site or edge of DES inflation. ST was classified based on the definitions established by the Academic Research Consortium.[9] Moderate-to-severe bleeding events were defined according to the GUSTO (Global Use of Strategies to Open Occluded Arteries) criteria. Procedural success was defined as a successful PCI without in-hospital major clinical complications including death, MI, and clinically driven target lesion revascularization. Device success was defined as the deployment of the study stent at the intended target lesion attaining final residual stenosis < 30% of the target lesion estimated both angiographically and through visual estimation.

Statistical analysis

Since there is no intervention, to study this cohort of patients we thought that the best method was to perform a descriptive analysis for an objective, comprehensive, and informative study of data. A a descriptive statistical analysis of the relevant variables was performed after collecting data. All statistical analyses were performed using the SPSS statistical software platform. Measures of central tendency such as means summarize the level of performance of a group of scores while measures of variability describe the spread of scores among the participants. Both are important to understand the behavior of this cohort. One provides information on the level of performance, and the other tells us how consistent that performance is. Categorical data were expressed as frequency and percentages. No further models were conducted as the idea of this paper was to describe a group of patients, not to compare groups or search for significant inter-group differences.

RESULTS

Baseline demographic and clinical characteristics

The data of 696 consecutive patients (742 BioMime stents implanted, 157 different stents) were collected in the study that mostly included males (80.1%). The baseline demographic and clinical characteristics of patients are shown on table 1. The patients' mean age was 64.6 ± 14 years. Conventional risk factors for CAD in the study population were diabetes mellitus (39%), hypertension (67.2%), dyslipidemia (64.8%), and active smoking (26.44%). The clinical status at admission is shown on table 1. Most patients (63.39%) had acute coronary syndrome.

Table 1. Baseline demographic and clinical characteristics

Patients	N = 696
Patients, demographics	
Age, years	64.6 ± 14
Male	556 (80.1)
Baseline past medical history	
Diabetes mellitus	271 (38.79)
Hypertension	466 (66.80)
Dyslipidemia	452 (64.80)
Active smoker	180 (26.44)
Previous CABG	57 (8.54)
Previous PCI	223 (32.07)
Vascular peripheral disease	69 (10.64)
Previous MI	181 (25.63)
Cardiac status at the index procedure	
Stable angina	254 (36.49)
Unstable angina	29 (4.16)
STEMI	227 (32.61)
NSTEMI	186 (26.72)
Left ventricular ejection fraction < 30%	181 (26)

CABG, coronary artery bypass graft; NSTEMI, non-ST-elevation acute myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.
Data are expressed as no. (%) or mean ± standard deviation.

Lesion and procedural characteristics

Out of a total of 899 lesions identified in 696 consecutive patients, 742 long and diffused de novo type C coronary lesions (1.07 lesions per patient) were successfully treated with long BioMime stents. No other stents were needed to treat the lesion initially handled with a long BioMime device. A total of 157 other lesions were treated with 157 different stents. Therefore, no overlapping was needed in any of the lesions treated with a long BioMime device. A total of 40% of the patients had 1-vessel disease, 37% 2-vessel disease and 23% of the patients had 3-vessel disease. The left anterior descending coronary artery followed by the right coronary artery were the main arteries treated. In 3.8% of the cases BioMime implantation involved the left main coronary artery. The mean length of the implanted BioMime SES system was 43.8 mm along with an average diameter of 3.1 mm. The immediate procedural and device success rates were 99.7% and 100%, respectively. The procedural variables are shown on table 2 and table 3.

Clinical outcomes at follow-up

Clinical follow-up was completed in 96.12% of the patients included at the 12-month follow-up. A total of 3.88% out of 696 patients were lost to follow-up after 12 months.

The cumulative incidence of MACE at the 1-, 6-, and 12-month follow-up was 2.2%, 6.6%, and 8.1%, respectively. The individual

Table 2. Lesion and procedural characteristics

Patients	N = 696
Total no. of lesions treated with the BioMime Morph SES system	742
Total no. of lesions treated with other stents	157
BioMime target lesion location	
Left anterior descending coronary artery	
Proximal LAD	146 (21.40)
Mid LAD	216 (30.80)
Distal LAD	28 (4.50)
Diagonal	11 (1.60)
Right coronary artery	
Proximal RCA	174 (25.10)
Mid RCA	257 (36.80)
Distal RCA	97 (14.10)
Left circumflex artery	
Proximal LCX	56 (8.20)
Mid LCX	90 (12.90)
Distal LCX	28 (4.10)
Left main coronary artery	26 (3.80)
Diseased vessel	1.84 ± 0.78

LAD, left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery; SES, sirolimus-eluting stent.
Data are expressed as no. (%).

Table 3. BioMime sirolimus-eluting stent system characteristics

Stent lenght (mm)	
37	100
40	189
44	128
48	325
Average stent length (mm)	43.80
Stent diameter (mm)	
2.25	42
2.5	153
2.75	84
3	263
3.5	185
4	13
4.5	2
Maximum pressure	
Predilatation	298 (86)
Postdilatation	376 (54)
Maximum pressure	14.6 ± 3.2
Average stent diamenter used (mm)	3.1

Data are expressed as no. (%).

Table 4. MACE at the follow-up

	% of patients	MACE
Follow-up		
1 month	682 (97.99)	13 (2.2)
6 to 9 months	675 (97.27)	44 (6.57)
12 months	668 (96.12)	53 (8.1)
MACE		
Bleeding at 1-M		20 (0.29)
Death at 1-M		41 (0.59)
MI at 1-M		41 (0.59)
Bleeding at 12-M		5 (0.75)
Death at 12-M		13 (2.09)
MI at 12-M		9 (1.34)
Total ST at 12-M		3 (0.50)

MACE, major adverse cardiovascular events; M, month; MI, myocardial infarction; ST, stent thrombosis.
Data are expressed as no. (%).

MACE at the follow-up are shown on table 4. The rates of cardiac death were 0.59% and 2.09% after 1 month and 1 year, respectively.

DISCUSSION

In the current study, the long nontapered BioMime SES system proved its safety and level of performance in consecutive real-world patients with long and diffused de novo coronary lesions. Despite the all-comers inclusion criteria defining a high-risk population, and the anatomical need for a long stent, procedural (99.7%) and device (100%) success were achieved and the clinical follow-up was quite favorable.

Studies have shown that the dimensions of coronary arteries taper naturally along with their length. They observed that 23% of the arteries had ≥ 1 mm taper and 19% arteries a 0.5 mm to 0.99 mm taper.[10] Stent sizing is critical for a successful PCI regarding the treatment of long tapered lesions. Stent oversizing (stents that are larger in diameter compared to the healthy artery) may induce pathological stress on the arterial wall, aneurysm formation, late ST, and even late perforations. Stent undersizing, on the other hand, (stents that are smaller in diameter compared to the healthy artery) may lead to ST due to stent malapposition.[11] Consistent with this, tapered stents were developed to potentially minimize clinical failure and maximize clinical benefits in these patients. This fact may be due to the specific design of the BioMime stents.

Ultrathin struts facilitate navegability, flexibility, and conformability of the vessel geometry while maintaining an excellent radial force. In addition, the open cell design throughout the entire body of the stent favors a less stiff device that follows more closely the

tapered contour of the artery resulting in less arterial wall stress. Compliant stents should be considered for tapered artery applications, perhaps even to avoid the need for tapered stents, at least up to 48 mm length, as shown in our data.[12-16]

The use of long coronary stents (≥ 30 mm), but not as long as the lesions treated in this registry, to treat long and diffuse native vessel disease, saphenous vein graft disease, and long coronary dissections is associated with a reasonable procedural success rate and acceptable early and intermediate-term clinical outcomes.[17] The treatment of very long CAD showed similar target lesion faliure at the 2-year follow-up for single DESs compared to overlapped DESs.[18] Our results suggest that both strategies are reasonable therapeutic options for patients with diffuse CAD. However, DES overlap occurs in > 10% of the patients treated with PCI in the routine clinical practice, and has been associated with impaired angiographic and long-term clinical outcomes including death or myocardial infarction.[19] In addition, the development of risk areas for malapposition with a single stent is significantly lower compared to overlapping stents. In cases where stent overlap cannot be avoided, deployment strategies should be optimized or new stent designs considered to reduce the risk of restenosis.[20] A single stent strategy is often more cost-effectiveness, and involves the administration of fewer contrast and fewer balloons. New designs of very long stents allow us not only to treat increasingly complex lesions, but also to simplify the procedure, and reduce the number of stents used with very favorable results, at least, similar to those obtained with overlapping stents.[21] Former studies have confirmed the safety and level of performance of the BioMime Morph, a very long tapered stent (60 mm) that can be considered the treatment of choice for very long and diffused tapered de novo coronary lesions in the routine clinical practice.[22] However, in long lesions treated with single stents of up to 48 mm in length, our results suggest that nontapered stents give very good clinical results.

Limitations

One limitation may be the follow-up period that may not be enough to determine the long-term safety and level of performance of long BioMime SES system in patients with long and diffused de novo coronary lesions.

CONCLUSIONS

This study confirmed the favorable procedural and device success, and the optimal safety outcomes reported at the follow up, of the long nontapered BioMime SES system, up to 48 mm length, in real-world patients with long and diffused de novo coronary lesions.

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AUTHORS' CONTRIBUTIONS

E. Domingo contributed to the study design, database completion, clinical follow-up, data analysis, and manuscript writing. J. Guindo contributed to the study design. R. Calviño Santos, J. Antoni Gomez, X. Carrillo, J. Sánchez, L. Andraka, A. Torres, J. Casanova-Sandoval, R. Ocaranza Sanchez, J. León Jiménez, J.F. Muñoz, R. Trillo Nouche, and M. Fuertes contributed to the database completion, and clinical follow-up. I. Otaegui contributed to the database completion, data analysis, and clinical follow-up. B. García del Balnco contributed to the study design, data analysis, and manuscript writing.

CONFLICTS OF INTEREST

None reported.

APPENDIX 1: STUDY INVESTIGATORS

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Original article

Simple option for large access vascular closure in case of failed suture-based closure device after TAVI

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ABSTRACT

Introduction and objectives: Vascular complications remain a potential problem after transcatheter aortic valve implantation (TAVI). Although suture-based vascular closure devices are most often used for vascular closure purposes, alternative plug-based vascular closure devices like the MANTA (Essential Medical Inc., United States) stand as a bail-out option for patients with failed suture-based closure devices. Since knowing the exact vessel depth is essential to use this device correctly before inserting the large introducer, we aimed to validate 2 different measurement techniques including preoperative multidetector computer tomography (MDCT) plus an alternative technique with the Angio-Seal device (Terumo Medical Corporation, United States) compared to a vendor specific measuring tool.
Methods: In patients eligible for TAVI, the depth of the femoral artery was measured preoperatively using MDCT, and then perioperatively with the Angio-Seal device. Both measurements were associated with the actual depth after puncture using the vendor-specific tool of the MANTA device.
Results: In a total of 168 patients treated with transfemoral TAVI, the depth of the vessel was measured both pre and perioperatively. The measurements obtained from the preoperative MDCT revealed the existence of a moderate correlation compared to the preoperative measurements obtained ($r = 0.64$; $P < .001$). Measurements obtained with the Angio-Seal device revealed a high correlation with the measuring tool included ($r = 0.99$; $P < .001$). Overall, 10 patients required the bail-out option with the MANTA device due to failed suture-based vascular closure devices.
Conclusions: In case of a failed suture-based vascular closure device after TAVI, the plug-based MANTA device can be used as a bail-out strategy. However, the measurement of the vessel depth obtained from preoperative MDCTs is not accurate enough for safe MANTA insertions. Measurements with the Angio-Seal device before inserting the large TAVI sheath stand as a simple solution to obtain exact measurements facilitating the use of the bail-out MANTA in case of failed suture-based closure vascular devices after TAVI.

Keywords: TAVI. Transfemoral. Access site complication. Vascular closure.

Una solución sencilla cuando fracasa el cierre con sutura en el acceso vascular del TAVI

RESUMEN

Introducción y objetivos: Entre las potenciales complicaciones del implante percutáneo de válvula aórtica (TAVI) se encuentran las complicaciones vasculares. Los dispositivos de sutura son los más utilizados para el cierre vascular, pero algunos sistemas de cierre con colágeno (MANTA, Essential Medical Inc., Estados Unidos) ofrecen una solución de rescate cuando los de sutura fallan. Para la correcta implantación de este dispositivo es necesario conocer la profundidad exacta de la arteria femoral antes de la inserción del introductor del TAVI. El objetivo de este estudio fue validar 2 técnicas diferentes de medida, la tomografía computarizada con multidetector (TCMD) y una técnica alternativa que emplea el dispositivo Angio-Seal (Terumo Medical Corporation, Estados Unidos), en comparación con el sistema específico de medida del dispositivo MANTA.
Métodos: En pacientes que recibieron TAVI, se midió la profundidad de la arteria femoral mediante TCMD antes y durante el procedimiento con un dispositivo Angio-Seal. Ambas medidas se correlacionaron con la real obtenida tras la punción mediante el medidor del dispositivo MANTA.

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Resultados: En 168 pacientes a quienes se realizó TAVI transfemoral, se midió la profundidad de la arteria femoral antes y durante el procedimiento. La medida con TCMD previa al procedimiento mostró una correlación moderada con las medidas durante el procedimiento (r = 0,64; p < 0,001). La medida con el dispositivo Angio-Seal mostró una alta correlación con la herramienta de medición (r = 0,99; p < 0,001). En total, 10 pacientes necesitaron rescate con dispositivo MANTA por fracaso de los dispositivos de sutura.
Conclusiones: En caso de fracaso de los dispositivos de sutura tras TAVI, el dispositivo de tapón de colágeno MANTA puede actuar como técnica de rescate. Sin embargo, la medida antes del procedimiento obtenida con TCMD no es precisa para implantar correctamente el dispositivo MANTA. La medición con un dispositivo Angio-Seal antes de la inserción del introductor del TAVI puede ser una solución sencilla para conocer las medidas con exactitud y para la inserción de rescate de un dispositivo MANTA, cuando fracasan los dispositivos de cierre por sutura.

Palabras clave: TAVI. Transfemoral. Complicaciones en punto de acceso. Cierre vascular.

Abbreviations

MDCT: multidetector computer tomography. **TAVI:** transcatheter aortic valve implantation.

INTRODUCTION

Despite growing experience and the development of new closure devices, the rates of vascular complications after transcatheter aortic valve implantation (TAVI) remain high (between 5% and 18%).[1-6] Recently, a new collagen plug-based device was recently introduced. Favorable results have been reported regarding the rate of vascular complications associated with this new collagen plug-based MANTA vascular closure device (Essential Medical Inc., United States) compared to suture-based devices.[7-9] However, due to several potential disadvantages (including major bleeding events with rates that go from 1% to 16%), limited data on future vessel accessibility, and significantly higher costs, the routine use of the new device has been put into question compared to suture-based devices.[7,10,11] Since puncture sites can safely be closed using suture-based devices, the new generation of plug-based systems may, therefore, be a valuable alternative as a bail-out strategy in case of failed suture-based devices.

However, one drawback of the MANTA system as a bail-out device is that it requires to know exactly the distance between the skin incision and the vessel for safe deployment and functionality purposes before inserting the large introducer sheath. Unfortunately, the vendor-specific measuring tool is not wrapped separately. Therefore, we aimed to validate 2 alternative measuring techniques including the preoperative multidetector computer tomography (MDCT), and the Angio-Seal device before inserting the large introducer sheath to get significant information of the depth of the vessel without having to unwrap the device.

METHODS

Patient and procedural characteristics

Patients agreed to the data retrospective anonymized analysis. A total of 168 consecutive patients with severe aortic stenosis scheduled for TAVI were included. All patients were evaluated by interdisciplinary heart teams. As a standard procedure all patients received MDCT to plan TAVI. All procedures were performed under local anesthesia. In all the cases both femoral arteries were used. One side for the TAVI sheath and the other for the pigtail catheter for the angiography plus a 7-Fr arterial line for hemodynamic monitoring. Routine closure follows with a Proglide closure device and a 6-Fr Angio-Seal device for the TAVI side plus a 6-Fr Angio-Seal for the contralateral side.

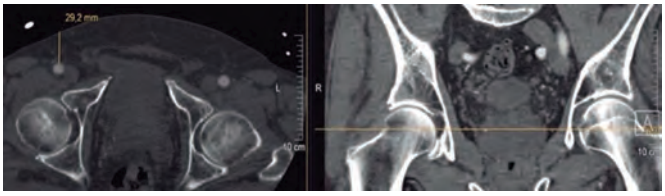

Figure 1. Measuring technique of the vessel depth at mid-hip head level (25 mm + 10 mm = 35 mm MANTA depth).

Measuring the depth of the vessel

Preoperatively, the depth of the vessel was measured using preoperative MDCT. The depth of the vessel was measured on a split screen using the Picture Archiving and Communication System imaging modality. In all the patients the measurements were obtained perpendicularly at skin level towards the femoral artery at mid-femoral head level (figure 1).

Perioperatively, measurements were obtained using the introducer sheath of a 6-Fr Angio-Seal device as follows. The introducer sheath reaches the vessel when bleeding through the indicator channel of the introducer sheath starts (figure 2A). In this position the letter or dot on the outside of the introducer sheath is noted and translated into distance using the schematic representation shown on figure 2B and table 1. According to the instructions for use of the MANTA vascular closure device, 1 cm had to be added. Then, the deployment depth of the MANTA device was noticed.[12]

Following these precautionary measures, 1 suture-based Proglide closure device was inserted and TAVI was performed as usual.

Vascular closure

During closure, operators aimed for systolic blood pressures < 160 mmHg. Heparin, and protamine were used at the operator's discretion. The delivery sheath was removed with a standard on-site wire

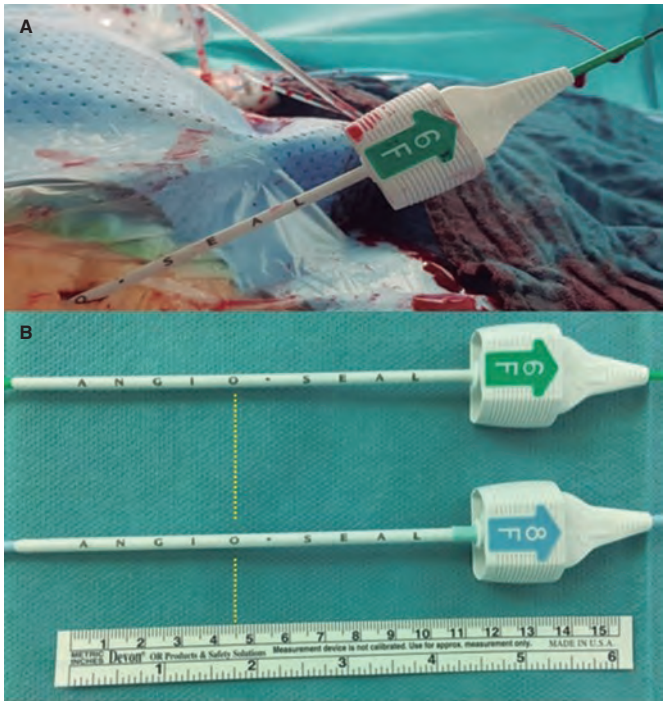

Figure 2. **A:** Measurement of the vessel depth equal to 'O'. **B:** Translation into distance using the scheme shown on table 1 eventually ending in a MANTA depth of 5.5 cm.

Table 1. Vessel depth measured using the Angio-Seal device. Eventually, 1 cm had to be added to be able to use the MANTA bail-out device

Angio-Seal	Vessel depth (cm)
A	0.5
N	1.5
G	2.5
I	3.5
O	4.5
*	5.5
S	6.5
E	7.5
A	8.5
L	9.5

while the access site was closed using the prepared Proglide system plus an additional 6-Fr Angio-Seal device. If the prepared suture-based system ruptures or in the presence of remaining severe bleeding following the insertion of the 8-Fr Angio-Seal introducer sheath, the introducer of the Angio-Seal was removed without implanting the plug, a MANTA vascular closure device was inserted, and then released based on the predefined vessel depth. The wire was removed after the final angiography to identify all possible access site-related complications. The contralateral side was closed using a 6-Fr Angio-Seal device.

A 300 mg clopidogrel loading dose was administered postoperatively, but not in patients already on clopidogrel. In patients on oral anticoagulants, therapy was interrupted prior to the procedure. All operators were familiar with all the vascular closure devices used.

Table 2. Baseline characteristics

Clinical characteristics	N = 168
Age (years)	83 [79.3-86.0]
Gender (male) (%)	66 (39.0%)
Body mass index (kg/m^2)	26.9 [24.2-30.5]
NYHA ≥ III (%)	144 (85.2)
Logistic EuroSCORE I (%)	16.8 [12.2-22.8]
Arterial hypertension (%)	152 (89.9%)
Coronary artery disease (%)	113 (66.8%)
s/p PCI (%)	62 (36.6%)
s/p CABG (%)	17 (10.1)
Atrial fibrillation (%)	67 (39.6)
Pulmonary hypertension (%)	12 (7.1%)
Diabetes mellitus (%)	59 (34.9%)
Peripheral artery disease (%)	29 (17.1%)
COPD (%)	34 (20.1%)
s/p stroke (%)	17 (10.1%)

CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; NYHA, New York Heart Association; s/p, status post.

Postoperative follow up

All patients received compression bandage at the puncture site for 6 hours and were monitored on an intermediate care unit for, at least, 24 hours. All the medical attention provided to the puncture site due to residual bleeding, and all postoperative imaging such as MDCT scan or duplex sonography were documented until hospital discharge.

Statistical analysis

The categorical variables were expressed as counts (percentages) while the continuous variables were expressed as median [interquartile range]. The correlation between measurements was estimated using Spearman's rank correlation coefficient.

The data supporting this study findings are available from the corresponding author upon reasonable request.

RESULTS

A total of 168 patients treated with transfemoral TAVI were included. Patients were typical TAVI patients. The patients' baseline characteristics are shown on table 2.

Measurements from preoperative MDCTs were obtained from all patients revealing a moderate correlation compared to perioperative measurements obtained using the vendor-specific MANTA measuring tool (r = 0.64; P < .001; figure 3).

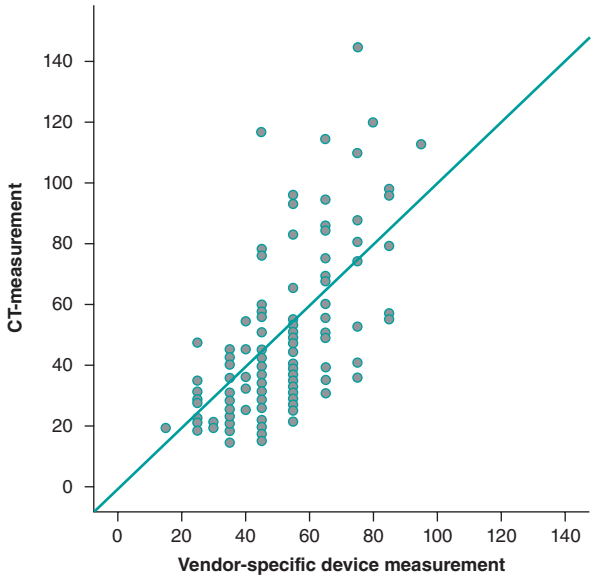

Figure 3. Correlation between the depth of the vessel measured on the previous multidetector computer tomography and on the vendor-specific measuring tool. CT, computed tomography.

Measurements using the Angio-Seal device were also successfully obtained from all patients revealing a high correlation with the vendor-specific MANTA measuring tool (r=0.99; $P < .001$).

Successful vascular closure was achieved in 158 cases using as a standard closure including the suture-based Proglide and the 6-Fr Angio-Seal device. The bail-out MANTA device was required in 10 patients (5.9%) due to Proglide suture rupture (n = 5) or remaining severe bleeding after insertion of the Angio-Seal introducer sheath (n = 5). The MANTA closure device was successfully inserted thanks to the measurements obtained with the Angio-Seal device before large sheath insertion. A total of 40 patients (23%) needed medical attention on the puncture site including prolonged pressure bandage or CT scan or duplex sonography. A total of 7 patients (4.1%) required postoperative surgery at the puncture site. One patient already carried a previous MANTA bail-out device that eventually led to a complete vascular occlusion due to known arterial occlusive disease. A total of 4 patients suffered a pseudoaneurysm after the routine use of the Proglide and the Angio-Seal that could not be treated by thrombin injection.

DISCUSSION

Although the rate of access site-related vascular complications after TAVI has decreased over the last few years, these complications are still associated with higher mortality and morbidity rates.[2,3,6,13] In this context, suture-based closure devices such as the Prostar or the Proglide are safe and effective widely used tools.[14] Although the use of the Prostar is associated with a lower risk of vascular stenosis, the use of the Proglide device has led to lower rates of adverse events such as device malfunction or residual bleeding.[2,13,15,16] However, both systems rely on a similar suture-based technique that demands careful preparation before the large delivery sheath can be inserted. The safe use of these closure devices after the insertion of large delivery sheaths is not possible anymore. Therefore, in case of closure device failure and severe bleeding, covered stent implantation using the cross-over technique or surgery to achieve hemostasis may be the only option left. Although the implantation of a covered stent graft is an effective treatment option for bleeding control, implanting covered stents using the cross-over technique can be challenging. Also, the external iliac and common femoral arteries are exposed to flexion of the hip joint, which may be associated with higher stent compression and fractures.[17-19] Additionally, the costs of covered stents are high.

Surgery should be spared as the last resort option only as it often needs to be performed under general anesthesia and the loss of blood is high until the surgical cut-down is prepared. Furthermore, wound infection or lymphatic fistulae may occur, thus delaying the patient's mobilization after TAVI, which may be associated with pneumonia or thrombosis.

Recently, a new plug-based closure device, the MANTA vascular closure device, has entered the clinical arena, and proved its efficacy and safety profile after TAVI. The first reports show rapid hemostasis and low rates of complications after implantation of the MANTA device, even lower compared to the Prostar and the Proglide vascular closure devices.[9] In contrast with this, a recently published randomized clinical trial showed similar results regarding access site bleedings compared to the Proglide system. However, while suture-based closure required additional closure devices more often like the Proglide or the Angio-Seal, the MANTA closure device numerically required complex maneuvers more often like covered stents or surgical bail-out strategies. The reason behind this may be the crossing of the wire through the toggle, which cannot be re-accessed using additional devices like the Angio-Seal or the Proglide.[20]

The considerably higher costs involved, 4 times more expensive compared to the Proglide, the unknown influence on the femoral artery wall, and re-access after device implantation have delayed the quick market penetration of this device as well as its routine use.

However, when using the MANTA vascular closure device, it is of utmost importance to measure the distance between the skin and the vessel accurately to ensure the precise placement of the anchor. During a scheduled MANTA procedure, this measurement is routinely obtained before the insertion of the large delivery sheath using a dedicated 8-Fr device that comes together with the MANTA device in the sterile package. This measurement may be cumbersome and yield inaccurate values if performed after the large sheath has been inserted given the degree of device-related bleeding. Therefore, we evaluated 2 different techniques to obtain this important data before the insertion of a large introducer device without having to unwrap the device to be prepared for a potential bail-out use. Compared with previous data we proved that a moderate correlation exists in the measurements obtained from preoperative MDCT only that were not good enough to allow the use of the MANTA device safely.[21] An inaccurate release of the system could lead to malapposition with persistent major bleeding especially in small or heavily calcified vessels or even to the vessel total occlusion. This inaccuracy may be explained by a smaller angle in the direction of the stitches compared to the perpendicular measurements obtained on the MDCT or to a different distribution or position of a skin flap in very obese patients during the MDCT and the procedure.

In contrast, the measurements obtained with the Angio-Seal device followed by an imaging-based predefinition of the corresponding MANTA implantation depth kept a close association with the measurements of the MANTA device. With this information, the femoral artery can be safely closed after a failed Proglide system. Unsolvable failed suture-based device with an additional Angio-Seal or Proglide due to severe bleeding or suture rupture occurred in 5.9% of the patients. Bail-out with MANTA insertion was successful in all patients. Only 1 patient required surgery due to a complete vascular occlusion (Thrombolysis in Myocardial Infarction grade-0

flow) associated with the MANTA device. In retrospect, a prior MDCT had revealed a very small vessel diameter and wall calcification at the puncture site. In these patients, a surgical cut-down would have been the access of choice.

The method presented here is also helpful in other clinical settings without prior MDCT in which large bore sheath are used such as delayed closures after emergency extracorporeal membrane oxygenation or Impella device placement (Abiomed Inc., United States). In these cases, a wire can be inserted through the arterial cannula or Impella CP introducer, and late vascular closure can then be safely achieved using a MANTA vascular closure device. To avoid the unpacking of the sterile device before the simple measuring method the use of an Angio-Seal is cost-effective, not time consuming, and provides information for future reference in case it is needed.

Limitations

The lack of randomization, and the small number of patients are obvious limitations of this study that should be taken into consideration when analyzing the data presented here.

CONCLUSIONS

Compared to MDCT measurements, the routine measurement of vessel depth using the Angio-Seal device stands as a simple option to obtain exact values to allow the bail-out use of the MANTA device in cases of failed suture-based closure device after TAVI. This method can also be used effectively in cases of delayed vascular closures of late explantations of the Impella device or emergency cannulations for venoarterial extracorporeal membrane oxygenation.

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AUTHORS' CONTRIBUTIONS

J. Blumenstein, T. Maruskin, O. Husser, and H. Möllmann contributed to the design, analysis, and writing of this manuscript. D. Sötemann, C. Eckel, C. Grothusen, G. Dohmen, C. Tesche, and H. Al.Terki contributed to both the writing and supervision of the manuscript.

CONFLICTS OF INTEREST

Neither one of the authors have made any disclosures regarding this manuscript, and they have all met all the requirements defined by the International Committee of Medical Journal Editors regarding the criteria for authorship of scientific articles.

WHAT IS KNOWN ABOUT THE TOPIC?

– Vascular closure can often be performed safely using suture-based devices after TAVI. However, suture ruptures or insufficient closures can directly lead to major vascular complications. In cases like this, closure can be performed using a different plug-based device (Manta Device). However, one drawback of this device is that it requires to know exactly the distance between the skin incision and the vessel for safe deployment and functionality purposes before inserting a large introducer sheath.

WHAT DOES THIS STUDY ADD?

– This study proved that preoperative MDCT obtained inappropriate measurements of the vessel depth. However, a new measuring technique can be established using an Angio-Seal device before inserting the large introducer sheath. In case of failed suture-based closures, the exact depth of the vessel should be known to be able to use a Manta device for bail-out closures. In addition, this technique can also be effectively in case of delayed vascular closures of late explantations of Impella devices or in cases of emergency cannulations for venoarterial extracorporeal membrane oxygenation.

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Special article

Renal denervation for the management of hypertension. Joint position statement from the SEH-LELHA and the ACI-SEC

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ABSTRACT

Hypertension is the most prevalent cardiovascular risk factor. Despite pharmacological treatment, a high percentage of patients do not achieve an adequate blood pressure control. Renal sympathetic denervation is a minimally invasive intervention for the management of hypertension involving the interruption of the renal artery sympathetic nervous system using a catheter-based approach. The early studies showed promising results, but the controversial results coming from the SYMPLICITY HTN-3 trial sent this technique into oblivion. Over the last 3 years, new clinical trials have appeared including new devices used in different populations, which definitively proves the effectiveness of renal sympathetic denervation.
This joint position statement from the Spanish Society of Hypertension-Spanish League for Combating High Blood Pressure (SEH-LELHA), and the Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC) reviews the evidence available on the efficacy and safety profile of renal sympathetic denervation for the management of hypertension. Based on the results of clinical trials, recommendations have been established on what patients may be eligible for renal sympathetic denervation and under what circumstances.

Keywords: Hypertension. Renal sympathetic denervation. Blood pressure.

Denervación renal en el tratamiento de la hipertensión arterial. Posicionamiento conjunto de la SEH-LELHA y la ACI-SEC

RESUMEN

La hipertensión arterial es el factor de riesgo cardiovascular más prevalente. A pesar del tratamiento farmacológico, un alto porcentaje de pacientes no consiguen un adecuado control. La denervación renal es una intervención mínimamente invasiva para el tratamiento de la hipertensión que implica la interrupción de los nervios simpáticos renales mediante un abordaje con catéter. Los estudios iniciales mostraron resultados prometedores, pero los controvertidos resultados del ensayo SYMPLICITY HTN-3 llevaron al abandono de la técnica. En los últimos 3 años han aparecido los resultados de nuevos ensayos clínicos, con nuevos dispositivos y en diferentes poblaciones, que demuestran definitivamente la eficacia de la denervación renal.
En este documento de posicionamiento conjunto de la Sociedad Española de Hipertensión-Liga Española para la Lucha contra la Hipertensión Arterial (SEH-LELHA) y la Asociación de Cardiología Intervencionista de la Sociedad Española de Cardiología (ACI-SEC)

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se revisa la evidencia disponible sobre la eficacia y la seguridad de la denervación renal en el tratamiento de la hipertensión. A partir de los resultados de los ensayos clínicos, se generan recomendaciones sobre qué pacientes y en qué condiciones podrían ser candidatos a una denervación renal.

Palabras clave: Hipertensión arterial. Denervación renal. Presión arterial.

Abbreviations

ABPM: ambulatory blood pressure monitoring. **BP:** blood pressure. **DBP:** diastolic blood pressure. **HMOD:** hypertension-mediated organ damage. **HTN:** hypertension. **RSD:** renal sympathetic denervation. **R-HTN:** resistant hypertension. **SBP:** systolic blood pressure.

INTRODUCTION

The role of the sympathetic nervous system in the pathophysiology of hypertension (HTN) is well known. In 2007, to address the unmet need of patients with resistant HTN (R-HTN), the first percutaneous renal sympathetic denervation (RSD) procedures were performed. First observational studies showed positive results, and the use of RSD started in select centers around the world.[1,2] However, in 2014, the publication of a study which did not demonstrate a greater efficacy of RSD vs a sham-control group to control blood pressure (BP)[3] dramatically reduced the interest of the scientific community in this procedure, as well as in its clinical application. An increased knowledge of renal anatomy combined with the development of second-generation devices has led to new studies, in which the efficacy of RSD vs a sham-control group has been demonstrated.[4-7] Although the road ahead is long, the new evidence provides a clear role for RSD in the management of patients with HTN.

The clinical practice guidelines on the management of hypertension published by the European Society of Cardiology and European Society of Hypertension (ESC/ESH) back in 2018 outlined the role of device-based approaches for the management of HTN in the context of clinical trials only.[8] The practical effect of this is that it discouraged the use of RSD. Despite the short time that has gone by since the publication of these guidelines, the data provided by the new clinical trials would justify treating selected patients with RSD.

This document reviews the evidence available on RSD for the management of HTN, analyzes possible indications, and suggests strategies to identify potentially eligible patients, formulated from the opinion of a panel of experts selected by the Spanish Society of Arterial Hypertension-Spanish League for the fight against Arterial Hypertension (SEH-LELHA), and the Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC). The writing of the document was carried out by professionals proposed by these scientific societies undersigning this work following their experience in the management of patients treated with RSD. After the first draft, other experts with and without previous experience in RSD carried out a critical review of the document, and agreed on the changes that were deemed appropriate.

CLINICAL EVIDENCE ON THE ROLE OF RENAL SYMPATHIC DENERVATION IN THE MANAGEMENT OF HYPERTENSION

The supplementary data shows the epidemiological characteristics of HTN (section 1), as well as the role of sympathetic nervous system in the management of HTN (section 2), thus improving our understanding of clinical trials. Table 1 of the supplementary data shows the main studies in which the efficacy of RSD has been assessed.

Back in 2009, the first study on RSD in patients with R-HTN, the SYMPLICITY HTN-1 trial, was published. This study suggested a high efficacy profile of RSD, and a lower office systolic blood pressure (SBP) down to 27 mmHg at 12 months, without any significant complications being reported.[1]

The SYMPLICITY HTN-3 trial was the first one to include a control group with a sham procedure and a 24-hour BP endpoint. No differences between the 2 treatment groups in terms of the efficacy profile of BP control in patients with R-HTN were reported at the 6-month follow-up.[3] The disagreement between the results of this study and the previous ones, as well as the identification of several confounding factors[9] brings up the need for designing new studies specifically aimed at solving these questions.

Definitive evidence on the efficacy of RSD has come from the SPYRAL HTN and RADIANCE-HTN studies. The SPYRAL HTN-ON MED trial enrolled patients with uncontrolled HTN treated with 1 to 3 antihypertensive drugs, randomized to receive RSD or a sham procedure. The 24-hour ambulatory SBP and diastolic BP (DBP) levels, as well as the office SBP and DBP levels dropped significantly in the RSD group compared to the sham control at the 6-month follow-up.[4] With a similar design, the SPYRAL HTN-OFF MED Pivotal trial enrolled uncontrolled hypertensive patients with office SBP levels between 150 mmHg and 180 mmHg in the absence of antihypertensive treatment. The 24-hour SBP and office SBP levels were reported at the 3-month follow-up.[5] The RADIANCE-HTN SOLO trial enrolled patients with HTN and ambulatory blood pressure monitoring (ABPM) levels ≥ 135/85 mmHg and ≤ 170/105 mmHg without pharmacological treatment. The 24-hour ambulatory SBP and DBP levels as well as the office SBP and DBP levels dropped significantly in the RSD group compared to the sham control at the 2-month follow-up.[6] The RADIANCE-HTN TRIO trial enrolled patients with R-HTN on a fixed-dose, single-pill combination of a calcium channel blocker, an angiotensin receptor blocker, plus a thiazide diuretic, randomized to receive ultrasound catheter-based RSD or a sham procedure. The 24-hour ambulatory SBP and DBP levels, as well as office SBP and DBP levels dropped significantly in the RSD group compared to the sham control at the 2-month follow-up.[7]

Real-life registries have enrolled more than 3500 patients treated with RSD showing lower office BP and ABPM levels. Some registries have demonstrated that the reduction of BP is not associated

with the medication burden or with an increased number of antihypertensive drugs. RSD has proven to be safe and has a low rate of complications associated with the procedure.[10] The GLOBAL SYMPLICITY registry, with over 2900 patients is the largest and longest duration analysis to this date of renal sympathetic denervation to show the efficacy and safety profile of RSD in a real-life scenario.[10] Table 2 of the supplementary data shows a summary of different registries on RSD.

RSD has been confirmed as a safe intervention. The incidence rate of both immediate complications associated with the procedure and renal and vascular complications in the short- and mid-term (6-12 months) is very low and is mainly associated with local problems at the puncture site; serious renal complications (renal artery dissection or stenosis) are anecdotal. Table 3 of the supplementary data summarizes the safety data from the main randomized clinical trials that often have a short-term clinical follow-up.

POSSIBLE INDICATIONS FOR RENAL SYMPATHETIC DENERVATION WITH DATA FROM THE LATEST CLINICAL TRIALS

Data from both randomized clinical trials and registries prove that the RSD procedure is safe and effective reducing BP, which is consistent across different populations including high-risk subgroups, and with different devices. Section 3 of the supplementary data reviews various consensus documents and recommendations previously published by different scientific societies prior to the publication of the SPYRAL HTN and RANDIANCE-HTN clinical trials.

RSD can be considered in patients with resistant HTN (BP > 140/90 mmHg despite lifestyle changes treated with ≥ 3 antihypertensive drugs at optimal doses, one of them being a diuretic or HTN controlled with ≥ 4 drugs),[8] and also in patients with uncontrolled HTN (BP > 140/90 mmHg in patients with poor therapeutic compliance), and high cardiovascular risk.

Renal sympathetic denervation in patients with resistant hypertension

Patients with R-HTN were the first group in whom the role of RSD was assessed. The SYMPLICITY HTN-3 trial failed to demonstrate the increased efficacy of RSD vs sham control in patients with R-HTN.[3] However, subsequent analysis revealed design and execution limitations that cast doubts on the reliability of the results.[9] In the recently published RADIANCE-HTN TRIO trial, patients with R-HTN treated with a standardized triple combination pill experienced a drop in their BP levels 2 months after RSD compared to a sham procedure.[7] If the BP lowering effect and the safety of RSD are maintained in the long term, RSD might be an alternative to the addition of more antihypertensive medications in patients with R-HTN.

Renal sympathetic denervation in patients with uncontrolled hypertension

The new evidence available introduces a paradigm shift for a technique that was initially conceived for the management of R-HTN when all other therapeutic options fail, and is currently an option that should be taken into consideration in patients with persistent BP > 140/90 mmHg despite drug treatment.

The concept of uncontrolled HTN includes a high percentage of hypertensive patients (maybe even > 60%) with highly heterogenous clinical characteristics and cardiovascular risk. Given the invasive nature of the RSD procedure, and until more information becomes available on the reduction of cardiovascular events in more specific subgroups of patients, there are some high-risk situations in which BP control is essential to reduce the risk of cardiovascular events:

a) Patients with frequent hypertensive crises. Hypertensive crises with SBP levels > 180 mmHg and/or DBP levels > 110 mmHg can cause brain, cardiac or microvascular damage. Emergency visits for hypertensive crises exceed 4% of all visits to the emergency room.[11] Even in the absence of hypertension-mediated organ damage (HMOD), episodes of hypertensive crisis can have long-term implications to the extent that these patients may have a 50% higher risk of suffering cardiovascular events compared to controlled hypertensive patients. Nonetheless, outside the crisis setting they show similar BP levels.[12]

b) Patients with low compliance to pharmacological treatment. Pharmacological treatment of HTN is generally a long-term option and in most cases, for life. Poor compliance is a common problem to the extent that almost one third of all hypertensive patients do not start a new prescription of antihypertensive drugs,[13] and around 50% become non-compliant within the first year after starting treatment.[13] In the SPYRAL HTN trials, the 24-hour ABPM levels showed decreased BP levels throughout the entire 24-hour period in patients treated with RSD compared to no changes in the control group in the absence of drugs or incomplete control in the presence of drugs.[4,5] Furthermore, in the SPYRAL HTN OFF-MED trial, the treatment group experienced an average reduction of 9.2 mmHg in office SBP levels.[5] A meta-analysis of 123 studies including 613 815 patients showed that a drop of office SBP levels of 10 mmHg was associated with a significantly lower risk of cardiovascular events.[14] Poor compliance is a serious problem of public health since these patients in whom an adequate BP control is not achieved, even due to poor therapeutic compliance, have a high cardiovascular risk.[15] However, we should stress that RSD alone cannot bring BP levels down enough to achieve BP control in most patients. In the RADIANCE-HTN SOLO trial, the 24-h ABPM only 25% of the patients treated with RSD reached values < 130/80 mmHg.[6] In these non-compliant patients, the main strength of RSD is the "always on" effect regardless of pharmacokinetics and compliance to drugs.

c) Patients with hypertension-mediated organ damage. The presence of HMOD identifies a group of patients with high cardiovascular risk in whom conventional treatment has failed to prevent the progression of the disease.[16] Achieving the BP levels recommended is especially important in these patients because, in the early stages of the disease, some types of HMOD can be reversed; in more advanced stages, HMOD is irreversible despite adequate BP control. But this is important since it slows its progression while reducing the cardiovascular risk of these high-risk patients.[17] A meta-analysis including 698 patients treated with RSD revealed an independent effect of RSD on HMOD, which advocates for the use of RSD in this group of high-risk patients.[18]

d) Patients at high cardiovascular risk. The European guidelines on the management of HTN establish the factors that influence cardiovascular risk in hypertensive patients including clinical characteristics, analytical characteristics, presence of HMOD or established cardiovascular or kidney disease. All these factors establish a 10-year cardiovascular risk that is categorized into 4 groups: low, moderate, high or very high risk to the extent that, for example, in high-risk patients the estimated cardiovascular mortality is 5% and in very high-risk patients > 10%.[8] The assessment of cardiovascular risk should play an important role in the decision-making process to the extent that the higher the risk, the greater the benefits expected with better BP control. Therefore patients at high or very high-risk would be eligible for RSD whenever BP control is not adequate.

Empowering the hypertensive patient in the setting of a shared decision-making process

Over the last few years, shared decision-making process has emerged as the go-to model in the management of different conditions. In the field of RSD, a recent survey revealed that 38% of hypertensive patients who still don't take antihypertensive medication would prefer RSD to lifelong drug therapy even knowing that it would probably not replace medication in many cases. Just this already reduces BP significantly.[19] With the evidence provided in recent trials, RSD could be a valid treatment option in patients with uncontrolled HTN and high to very-high cardiovascular risk in whom, in a shared decision-making process context, consensus with the patient can be reached. In any case, we should mention that the treatment of HTN always requires the adoption of healthy lifestyle habits, and the recommendation to patients should include drug treatment as the first option.

STUDY PRIOR TO RENAL SYMPATHETIC DENERVATION

Patients should be examined in a unit specialized in HTN and vascular risk 3 months prior to the procedure in a center with proven experience.[20] Table 1 summarizes the studies to be conducted in patients eligible for RSD.

Uncontrolled HTN should be confirmed through 24-hour ABPM.[21] After confirming the presence of uncontrolled HTN, the clinical situations that increase BP levels such as obesity or obstructive sleep apnea should be identified and corrected. Also, substances such as salt or certain drugs that may also lead to HTN should be suspended or minimized. Non-compliance to treatment, which is very common and not always identified by the patient, if not rigorously investigated, should be ruled out.[22] It is essential to rule out secondary HTN (table 2) or, if diagnosed, treat it effectively. Still, it is not an absolute contraindication to RSD.[23]

RENAL SYMPATHETIC DENERVATION PROCEDURE WITH RADIOFREQUENCY DEVICES

Section 4 of the supplementary data shows more in-depth technical aspects of RSD. Figure 1 of the supplementary data summarizes the RSD procedure.

A better knowledge of the anatomy of renal nerves[24] and the development of new ablation devices have optimized the treatment technique,[5,6] which is based on 3 main objectives:

Management of the renal artery main trunk and branches

It is common for the renal nerves to reach the kidney after bypassing the main renal artery.[24] In animal models, it has also been confirmed that the application of combined radiofrequency in the renal artery main trunk and branches reduced the content of norepinephrine in the renal tissue even more, and in the cortical axonal density, both associated with the response to RSD.[25]

In patients treated with RSD, the presence of untreated accessory arteries leads to a lower hypotensive response.[26] Their identification and treatment is essential and, if they are amenable to treatment thanks to their diameter (minimum diameters of 3 mm), the treatment of accessory arteries is advised.

Last but not least, the perivascular space around the ostium and the proximal third of the main renal artery is often occupied by ganglia of solar plexus and by the lumbar sympathetic chain (figure 1). Both carry innervation to the kidneys, but also to other abdominal and pelvic organs, and they could be accidentally denervated if the treatment is applied to the ostium and proximal third of the main renal artery. Therefore, until more information becomes available, it seems reasonable to be cautious when treating the most ostial portion of renal arteries.[24]

Table 1. Studies prior to renal sympathetic denervation in patients with uncontrolled hypertension

Evaluation of pharmacological treatment
Type and number of drugs
Drug adequate dosage
Assess use of aldosterone antagonist
Assess lack of therapy compliance
Assess intolerance to drug therapy
24-hour ABPM study
Rule out pseudo-resistant hypertension or white coat effect
Confirm uncontrolled hypertension (SBP > 130 mmHg/DBP > 80 mmHg at the 24-hour levels or SBP > 135/DBP > 85 in the day's levels)
Rule out secondary causes of hypertension (table 2)
Cardiovascular risk assessment
Coexistence of other cardiovascular risk factors such as dyslipidemia, diabetes or smoking
Presence of HMOD
Presence of established cardiovascular or kidney disease
Imaging of the renal anatomy by computerized tomography or nuclear magnetic resonance imaging (assessment of occlusive stenosis, accessory branches, arterial diameter)
Complementary tests recommended:
Hemogram, renal function parameters, liver and lipid profiles, and urine sediment tests to detect the presence of microalbuminuria
Specific analytical determinations:
Baseline plasma aldosterone-to-renin ratio
Thyroid hormones
Calcium-phosphorus metabolism with parathyroid hormone levels
Cortisol (basal and 24-hour urine ratios)
Catecholamines with 24-hour urinary metanephrines ratio
Polysomnography

ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure, HMOD, hypertension-mediated organ damage; SBP, systolic blood pressure.

Treatment of the 4 quadrants of the renal artery

The distribution of nerve fibers around the renal artery follows a variable pattern across different individuals.[27] Preclinical studies in a porcine model have shown that the application of radiofrequency in one point produces effects on approximately 25% of the arterial circumference,[27] and procedures that use multiple helically staggered ablations in the 4 quadrants are more effective reducing the norepinephrine content into the renal tissue.[28]

Table 2. Causes of secondary hypertension

Renal parenchymal diseases	Glomerulopathies Polycystic disease Renal tumors Obstructive uropathy
Renovascular diseases	Fibrodysplasia Atherosclerosis
Suprarrenal diseases	Primary hyperaldosteronism Cushing's syndrome 17-alpha-hydroxylase deficiency Pheochromocytoma Apparent excess of mineralocorticoids
Vasculares diseases	Aortic coarctation Large vessel vasculitis
Endocrine-metabolic	Thyroid dysfunction Hyperparathyroidism Acromegaly
Neurological diseases	Dysautonomia Intracranial hypertension Psychogenic
Toxic-pharmacological diseases	Corticosteroids Non-steroidal anti-inflammatory drugs Cyclosporines Tricyclic antidepressants Anovulatory drugs Erythropoietin Licorice Cocaine High doses of caffeine
Genetic diseases	Monogenic forms Liddle syndrome

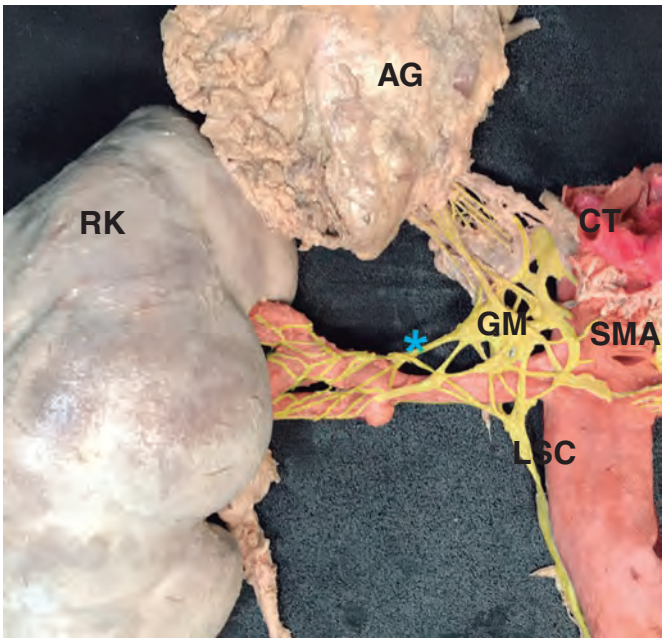

Figure 1. Detail of renal sympathetic innervation. Renal nerves are usually arranged in large bundles and only form a true plexus when they are close to entering the kidney. Some nerves bypass the main renal artery and join distally to the different arterial divisions of the main renal artery (late arrival nerves). In this case, a late arrival nerve is seen joining the proximal third of the anterior division of the main renal artery (blue asterisk). It can also be seen how the proximal main renal artery is occupied by fused ganglia of the solar plexus (GM), and by the lumbar sympathetic chain (LSC). Both provide innervation to the kidneys, but also to other abdominal and pelvic organs, which can be accidentally denervated if the proximal third of the main renal artery is treated. The image also shows that the maximum proximity of nerve fibers to the arterial wall mainly occurs at branch level, but also at main trunk level. This is the target area of treatment, always avoiding the application of radiofrequency at renal pelvis level. AG, adrenal gland; CT, celiac trunk; GM, ganglionic mass made up of the aorticorenal and celiac ganglia; LSC, lumbar sympathetic chain; RK, right kidney; SMA, superior mesenteric artery; blue asterisk, late arrival nerve. In red, arterial structures. In yellow, nervous tissue.

Application of the maximum possible number of ablation points

A post-hoc analysis of the SYMPLICITY HTN-3 trial confirmed that patients with a greater number of radiofrequency applications reduced their BP levels even more without any associated adverse events.[9] We recommend applying the maximum number of ablation points possible, always respecting a distance of 5 mm among them with a 4-quadrant distribution.

Section 4 of the supplementary data shows how to perform a RSD procedure using a tetrapolar radiofrequency catheter. Table 3 shows the precautions and contraindications regarding RSD.

Care after renal sympathetic denervation procedure

Once the procedure is finished, it is important to ensure adequate hemostasis in the femoral puncture. Usually, in the absence of complications, patients can be discharged after 24 to 48 hours with the same antihypertensive treatment they had before the procedure or with treatment adjustments in cases that show an immediate response, but still with adjustment appointments within 5 to 7 days. Of note, the effects of the intervention can take weeks to materialize.[29]

CLINICAL MANAGEMENT AFTER RENAL SYMPATHETIC DENERVATION

The main objective of the follow-up should be to confirm the safety of the intervention and the absence of complications in the short-, mid-, and long-term follow-up, as well as to monitor the evolution of BP levels and the adjustment of drug treatment.

At the clinical follow-up, it is important to maintain a multidisciplinary team same as during the selection of candidates. Table 4 shows the clinical management after RSD.

REQUIREMENTS OF A RENAL SYMPATHETIC DENERVATION PROGRAM

The success of a RSD program is based on the existence of a multidisciplinary team that performs a comprehensive assessment of the patient from the selection of candidates through their assessment prior to the intervention, the RSD procedure, and subsequent follow-up. This process should be carried out at specific units specialized in the management of HTN in collaboration with interventional cardiology units. Figure 2 shows the selection process of eligible patients.

We strongly discourage isolated procedures outside this controlled environment. RSD should not be performed in centers with volumes < 10 cases/year. Centers without a structured RSD program, but

Table 3. Precautions and contraindications to renal sympathetic denervation

• Renal sympathetic denervation has not been evaluated in patients who are pregnant, nursing, intend to become pregnant or in patients with type I diabetes mellitus, previous renal angioplasty, indwelling ureteral stents, aortic grafts or abnormal renal anatomy
• Subjects in whom a reduction of blood pressure would be considered hazardous (such as those with hemodynamically significant valvular heart disease)
• Implantable pacemakers and implantable cardioverter/defibrillators may be adversely affected by radiofrequency ablation. Consider deactivating implantable cardioverter/defibrillators during ablation, have temporary external sources of pacing and defibrillation available during ablation, and perform a complete analysis of the functionality of the device implanted after ablation
• Avoid treating arteries with diameters < 3 mm or > 8 mm
• Avoid treating arteries with significant disease or flow-limiting obstructions

Table 4. Clinical management after renal sympathetic denervation*

Blood pressure control
Home self-measurement of blood pressure is recommended to assess blood pressure decrease
Patient education to detect symptoms of hypotension
Pharmacological de-escalation, when appropriate
24-hour ambulatory blood pressure monitoring levels at 3-6 months to assess response to RSD
24-hour ambulatory blood pressure monitoring levels to assess long-term durability of renal sympathetic denervation
Renal function: in patients at risk of contrast nephropathy, control should follow after 7-10 days (individualize based on the clinical criteria)
Routine renal imaging modalities (echocardiography, computed tomography scan, magnetic resonance imaging) are ill-advised

* Control after renal sympathetic denervation should be performed in a hypertension-specific unit as part of a regulated renal sympathetic denervation program.

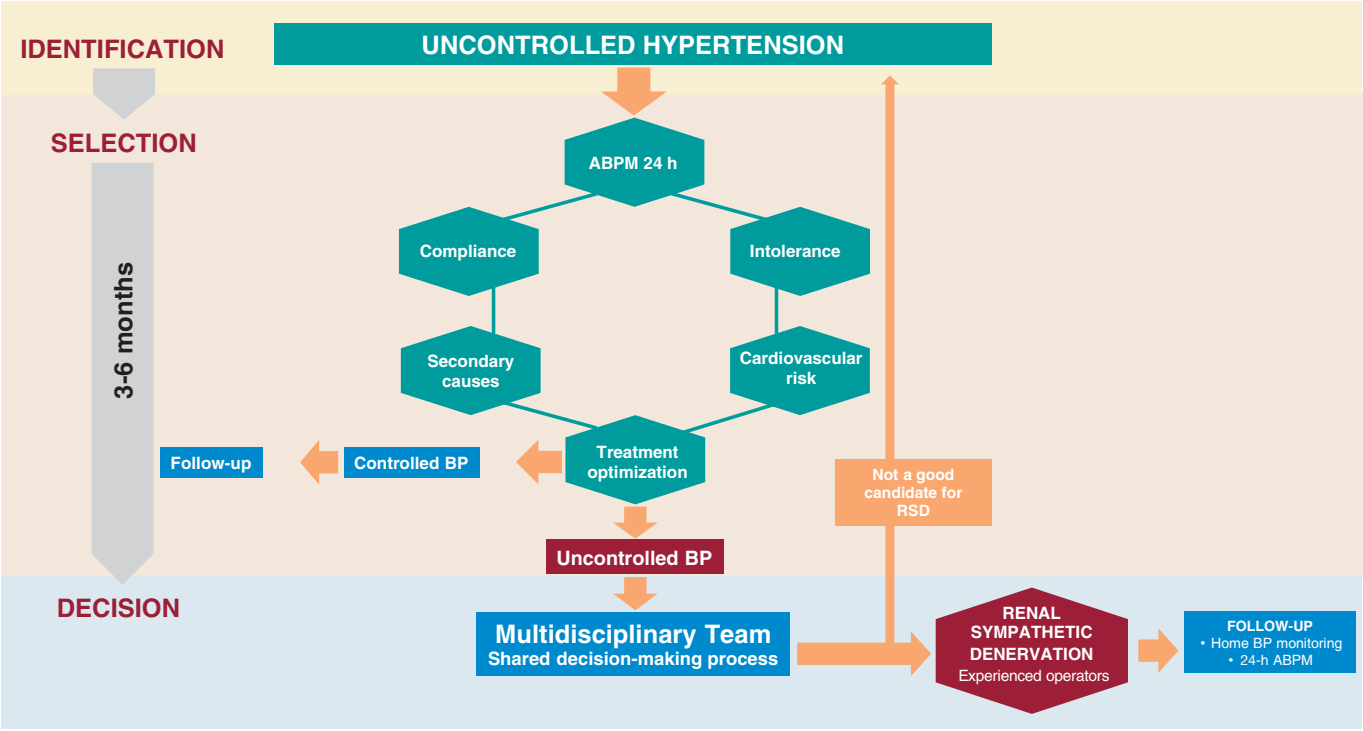

Figure 2. Identification process, patient selection and decision on RDN. Patients with uncontrolled HTN (BP > 140/90 mmHg despite treatment) should be evaluated in an HTN unit. The lack of control should be confirmed by ABPM, assess adherence/intolerance to drugs, rule out secondary causes and cardiovascular risk. If, after optimizing the treatment, the lack of control persists, in patients at high or very high risk, and in a shared-decision process with the patient, RDN may be indicated. Adherence is defined as the extent to which a person's behavior —taking medication, following a diet, and/or executing lifestyle changes— corresponds with the agreed recommendations from a healthcare provider. Drug intolerance refers to an inability to tolerate the adverse effects of a medication, generally at therapeutic or subtherapeutic doses. Treatment optimization refers to lifestyle changes and pharmacological recommendations, including target doses, recommended by clinical practice guidelines.[8] ABPM, ambulatory blood pressure monitoring; BP, blood pressure; RSD: renal sympathetic denervation.

with eligible patients, should refer them to an experienced center rather than performing isolated procedures.

RSD procedures should be performed by operators experienced in the management of endovascular treatment. The SYMPLICITY HTN-3 trial post-hoc analysis showed the importance of an experienced interventional specialist given one of the factors influencing the results of the study was the operator's lack of experience.[9] Therefore, we recommend that procedures should be performed at centers with proven experience only and that, in centers that lack

this experience, the possibility of monitoring should be available including assistance during the patient selection process and supervision of the procedure until enough experience is gained to ensure optimal results.

CONCLUSIONS

This expert consensus document has reviewed the information available regarding RSD in the management of patients with HTN. Also, it has established, for the first time, the indication for RSD in cases of uncontrolled HTN, especially in patients at high cardiovascular risk with HMOD or cardiovascular disease while taking the patient's opinion into consideration as part of a shared decision-making process, and as long as it is evaluated by a multidisciplinary team and performed by experienced operators.

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AUTHORS' CONTRIBUTIONS

Study concept and design: O. Rodríguez-Leor, and J.A. García-Donaire; manuscript writing: O. Rodríguez-Leor, F. Jaén-Águila, J. Segura, I. J. Nuñez-Gil, A. García-Touchard, E. Rubio, M. Troya, J. Diego-Mediavilla, and J.A. García-Donaire; critical review: O. Rodríguez-Leor, Á. Cequier, R. Moreno, N. Martell, P. Beltrán, and E. Molina.

CONFLICTS OF INTEREST

O. Rodríguez-Leor, and J. A. García-Donaire have received personal fees from Medtronic, outside the submitted work. A. García-Touchard reports having received grants from Medtronic, and personal fees from Medtronic, also outside the submitted work. Á. Cequier reports having received grants and personal fees from Abbott Vascular, grants, and personal fees from Biosensors, grants from Boston Scientific, grants, and personal fees from Medtronic, grants from Biomenco, Cordis, Orbus Neich, and from the Spain Society of Cardiology, personal fees from Ferrer International, Terumo, Astra Zeneca, and from Biotronik outside the submitted work. R. Moreno is associate editor of *REC: Interventional Cardiology*. The journal's editorial procedure to ensure impartial handling of the manuscript has been followed. F. Jaén-Águila, J. Segura, I. J. Núñez-Gil, E. Rubio, M. Troya, J. Diego-Mediavilla, R. Moreno, N. Martell, P. Beltrán, and E. Molina declared no relationship whatsoever relevant to the contents of this paper worthy of disclosure.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M21000235.

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Review article

Intraoperative echocardiographic assessment of mitral regurgitation after mitral clip implantation: literature review

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ABSTRACT

Initially, percutaneous mitral clip emerges as an alternative to surgery in patients with severe mitral regurgitation (MR) and high surgical risk. Nonetheless, it is now also considered a first-line treatment in patients with left ventricular ejection fractions somewhere between 20% and 50%, end-systolic diameters < 70 mm, and pulmonary systolic pressures < 70 mmHg. Successful results depend on reducing the severity of MR. The common parameters used to evaluate native MR have not been properly validated in this context. Therefore, the parameters that should be used to quantify residual MR during intraprocedural transesophageal echocardiography are still under discussion. There is scarce evidence and no validation studies. Although these have limitations, color Doppler echocardiography, proximal isovelocity surface area (PISA) and its derived area, continuous-wave Doppler signal, transmitral flow, and regurgitant flow are not accurate parameters to quantify residual MR due to clip artifacts. On the other hand, the width of the vena contracta, the 3D-vena contracta area, and pulmonary venous flow are associated with a satisfactory approach. Using a comprehensive method is the most practical thing to do.

Keywords: Mitral clip. Mitral regurgitation. Intraoperative transesophageal echocardiography. Mitral regurgitation assessment.

Valoración ecocardiográfica intraprocedimiento de insuficiencia mitral posimplante de clip: revisión bibliográfica

RESUMEN

Inicialmente el clip mitral surge como alternativa a la cirugía en pacientes con insuficiencia mitral (IM) grave y alto riesgo quirúrgico. Sin embargo, recientemente se ha posicionado también como tratamiento de primera línea en pacientes con fracción de eyección del ventrículo izquierdo del 20-50%, con diámetro telesistólico ventricular izquierdo < 70 mm y presión sistólica pulmonar < 70 mmHg. Su éxito depende de la disminución de la gravedad de la IM. Los parámetros usados para cuantificar la IM nativa no se han validado de manera adecuada en presencia de clip, por lo que resulta controvertido establecer cuál es el método de elección para valorar la IM residual en la ecocardiografía transesofágica intraprocedimiento. La escasa evidencia disponible carece de estudios de validación. Pese a sus limitaciones, parece que el Doppler color, el área de superficie de isovelocidad proximal y su área derivada, la señal del Doppler continuo, el flujo transmitral y el volumen regurgitante no son fiables debido a los artefactos producidos por el clip. La combinación de la anchura de la vena contracta, el área de la vena contracta medida por ecografía tridimensional y el patrón del flujo en las venas pulmonares parece arrojar resultados satisfactorios. La evaluación integral con varios parámetros es lo más completo.

Palabras clave: Clip mitral. Insuficiencia mitral. Ecocardiografía transesofágica intraprocedimiento. Cuantificación de la insuficiencia mitral.

Abbreviations

IM: insuficiencia mitral. **PISA:** área de isovelocidad proximal. **ETE:** ecocardiografía transesofágica.

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INTRODUCTION

Percutaneous mitral repair with clip initially started as a therapeutic alternative to mitral valve surgery in cases of unacceptable surgical risk and severe, symptomatic mitral regurgitation (MR).[1,2] Based on the latest scientific evidence available, the European Society of Cardiology and the American Heart Association consider the clip as the first-line therapy for patients with severe, symptomatic MR despite the optimal medical therapy, left ventricular ejection fraction between 20% and 50%, left ventricular end-diastolic diameter < 70 mm, and pulmonary artery systolic pressure < 70 mmHg.[3,4] The procedure is based on the central approximation of the free edges of the leaflets to create a double orifice on both sides of the device.[5]

Quantifying MR on the native valve is challenging in routine clinical practice due to the valve morphology (oval-shaped, 2 commissures in different planes, divided into 3 anterior and 3 posterior scallops), due to the limitations of two- and three-dimensional (2D and 3D) transthoracic and transesophageal echocardiography with respect to the orientation of the transducer and the plane slices, and because it is an operator-dependent technique. If the valve morphology changes after clip implantation, quantifying MR is even more difficult to accomplish.

When the clip comes near the free edges of the anterior and posterior central scallops (A2-P2) a series of changes occur in the coaptation point that impact the quantification of MR (figure 1[6]): *a)* 2 or more regurgitant orifices are created (depending on the number of clips implanted) in the coaptation line adjacent to the device; *b)* the new orifices created show irregular geometries, which means that no circular or elliptical geometric assumptions should be made to this point; *c)* the device generates acoustic shadowing on the valve that interferes with the color Doppler echocardiography images (figure 2).[7]

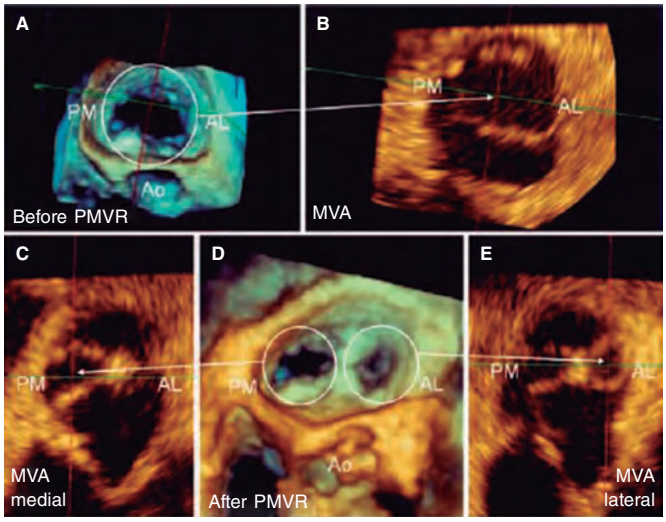

Figure 1. Three-dimensional transesophageal echocardiography image. **A:** mitral valve area (MVA) before percutaneous repair (Before PMVR) seen inside the circle. **B:** anterolateral (AL), and posteromedial (PM) commissure before clip implantation. The mitral valve area is shown here with an arrow. **C:** mitral valve area of the medial orifice (medial MVA) after clip implantation (shown by the arrow) outlined by the posteromedial (PL) commissure. **D:** double residual orifice after clip implantation (after PMVR); both the PM, and the AL are shown with circles. **E:** mitral valve area of the residual lateral orifice (lateral MVA) after clip implantation (shown by the arrow) and outlined by the AL commissure. Both residual orifices are found in different projections. Ao, aorta. Reproduced with permission from Ikenaga et al.[5].

For this reason, the traditional assessment parameters of MR should not be applied to residual MR after clip implantation. However, a proper assessment is of paramount importance not only because it is key to a successful procedure, but also because it has prognostic value.[8] Residual MR > 2/4 increases the risk of major adverse cardiovascular events, cardiac death, and mitral valve surgery or new percutaneous repair with clip implantation. Also, it is associated with a higher risk of disease progression in time, more symptoms, and a worse survival rate at the 12-month follow-up.[8-11] On the other hand, implanting excessive clips can increase the transmitral gradient and cause mitral stenosis, which also increases the mortality rate at 12 months.[12,13] Despite this prognostic significance there is no gold standard or guidelines with detailed recommendations based on observational trials or on assessments made by expert operators.

The initial trials (EVEREST I,[14] COAPT,[15] and MITRA-FR[16]) took measurements in core laboratories. In the case of the EVEREST I trial,[14] the severity of residual MR was assessed using the color Doppler jet area, the pulmonary venous (PV) flow pattern, the regurgitant volume, and the regurgitant fraction. It is specifically described that neither the proximal isovelocity surface area (PISA) nor the vena contracta width (VCW) are used due to the visual limitations associated with the device when interfering with the image (figure 2).[7] The COAPT trial specifies that the PISA was not obtained for the same reason. Also, that for the VCW, in case of multiple jets, the width of the predominant jet was selected or the widths of all the jets were added.[17] However, the MITRA-FR trial only reported on the effective orifice area in 2D, and the regurgitant volume.[16] There seem to be obvious disparities in the parameters used, reflecting the lack of consensus in this regard.

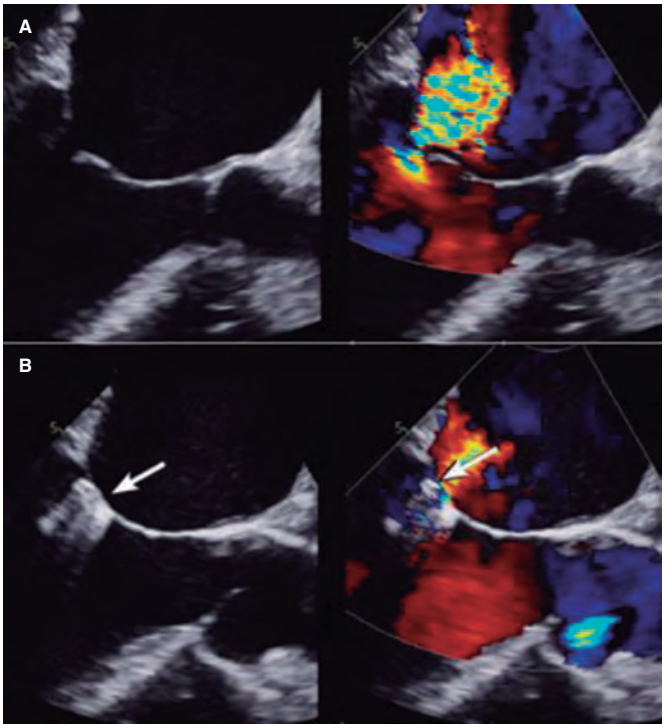

Figure 2. Two-dimensional transesophageal echocardiography image. **A:** mitral regurgitation before clip implantation. **B:** the clip appears like acoustic shadowing. The color image shows how difficult it is to assess the radius of the proximal isovelocity surface area (PISA) and the vena contracta due to clip interference (shown by the arrow). Reproduced with permission from Mayo Clinic.[7]

Results from scientific evidence are sometimes controversial. Only the guidelines published by the American Society of Echocardiography back in 2019[2] are available plus an expert consensus reached by the European Society of Echocardiography and the American Society of Echocardiography.[18] Based on these documents, recommendations advocate for assessing regurgitation using transesophageal echocardiography (TEE) both intraoperative and immediately after the procedure while always bearing in mind the effect of sedation or general anesthesia.[2] These guidelines give orientations on how to assess the severity of residual MR. However, no specific instructions are provided, leading to variable results in every center and leaving assessments to the operator's experience.

METHODS

A bibliographic search was conducted on the main international databases (PubMed, Embase, and Cochrane) using the following MeSH terms: "mitral regurgitation AND MitraClip AND echocardiographic assessment", "severity of residual mitral regurgitation after MitraClip", "3D vena contracta area after MitraClip", "TEE vena contracta after MitraClip", "vena contracta area and MitraClip", "vena contracta area after MitraClip", "pulmonary venous flow after MitraClip", "MitraClip and pulmonary flow"," pulmonary venous flow and prediction of MitraClip", "continuous doppler mitral regurgitation after MitraClip", "mitral regurgitation doppler signal after MitraClip", "doppler wave after MitraClip", "transmitral doppler after MitraClip", "E-wave after MitraClip", "spontaneous contrast in LA after MitraClip", "ratio VTI mitral and VTI LVOT after MitraClip", "stroke volume after MitraClip", "PISA after MitraClip", and "EROA and PISA and MitraClip". Filters in both English and Spanish were used without age limitations.

RESULTS

Evidence is based on small or mid-sized observational trials that use the assessments made by an expert operator or the parameters established by original—still unvalidated—trials as the reference standard. Based on the most recent consensus recommendations[2] the specific evidence behind each parameter is described below:

Color Doppler echocardiography

It is a visual estimation of the size, number, origin, and direction of the jets. It often overestimates severity in case of multiple jets and underestimates it in case of eccentric jets.[19] Still, it provides an early scan of regurgitant jets. Lin, et al.,[20] and Altiok, et al.[6] exposed that, although the regurgitant volume of MR is still the same due to 1 or multiple jets, the color Doppler jet area looks bigger with multiple jets, which leads to overestimating severity (figure 3).[20] For these reasons, it is often discarded as an isolated parameter in clinical trials.

Flow convergence region (the PISA radius)

To estimate the PISA radius-derived effective regurgitant orifice area (ROA) isovelocity hemispheres of convergent flow need to be created. When a clip stands in the way, these hemispheres cannot be created and the measurement is technically wrong.[2] Therefore, in the case of multiple jets, eccentric jets or significant acoustic shadowing, severity is often under- or overestimated. The severity of regurgitation based on the sum of several PISAs has not been defined, which is why it cannot be used. Because of all these limitations, the early studies on percutaneous mitral valve repair with mitral clip[14-16] did not include the study of the PISA (figure 2 and figure 4)[7,21].

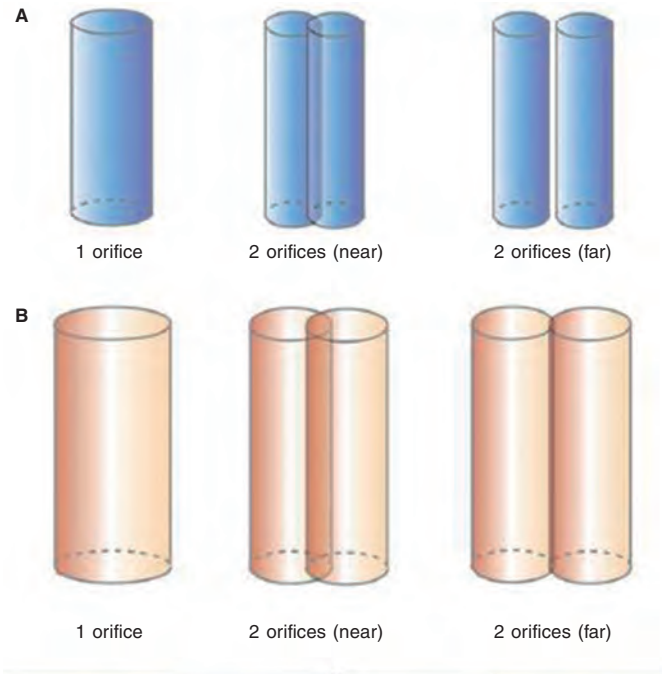

Figure 3. Impact of flow dynamics in the color Doppler jet area. The regurgitant volume from the ventricle towards the atrium creates interphase velocity between the former and atrial blood that generates surface shear stress where blood vortices that take more blood around them are produced. The color Doppler jet area looks magnified compared to the early regurgitant volume. **A** and **B** show that when the same regurgitant volume passes through 2 nearby or distant orifices with respect to one another, both jets merge due to the formation of vortices thus giving the impression of more severity. **C** and **D** show that for any given volume (eg, 10 mL), the number of pixels generated based on the number of orifices duplicates. Reproduced with permission from Lin et al.[20].

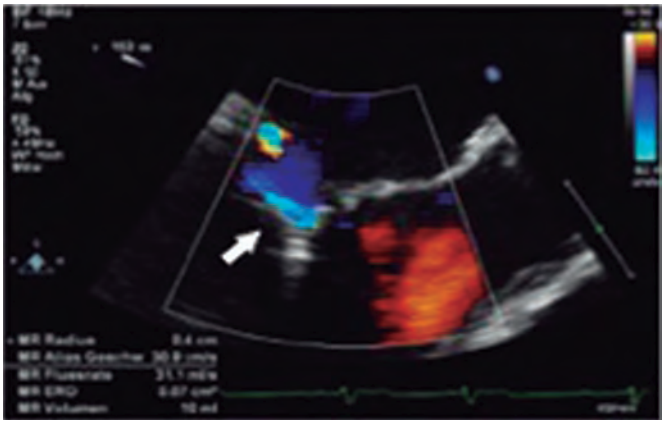

Figure 4. Two-dimensional transesophageal echocardiography image. Presence of acoustic shadowing due to clip implantation (arrow). Reproduced with permission from Lesevic et al.[21].

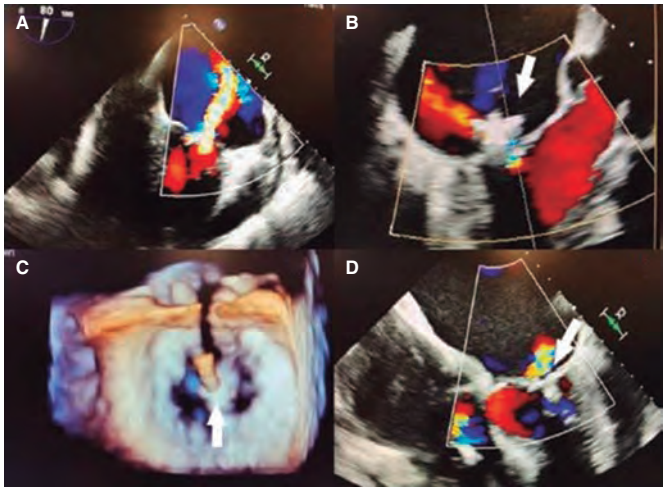

Figure 5. Two- and three-dimensional transesophageal echocardiography images. **A:** severe early mitral regurgitation. **B:** residual mitral regurgitation after clip implantation showing the clip interference (arrow) by just looking at the vena contracta. **C:** three-dimensional image of the clip (arrow) and the 2 residual orifices. **D:** color Doppler showing residual mitral regurgitation without visualization of vena contracta due to clip interference (arrow). Reproduced with permission from Elbey et al.[22].

Vena contracta width

If the regurgitant orifice cannot be clearly seen (small or eccentric jet, clip interference), this measure can come with an artifact (figure 5).[22] It should be used carefully because it has not been validated yet or severity values established in case of multiple jets.[14] To this date, no specific studies have been conducted supporting this parameter. The American guidelines[2] only establish that a value ≥ 7 mm is specific of severity and since the COAPT trial used it in its assessment of residual MR,[17] in practice, it could be used, especially in case of a predominant non-eccentric regurgitant jet. With eccentric jets, this measurement was less reliable (similar to native MR), which is why averaging several beats is advised,[2] and why its use as an isolated parameter is ill-advised.

Three-dimensional vena contracta area

It allows us to better outline the regurgitant orifice, but with an associated risk of blooming artifacts (overexpression of the area when the Doppler color gain is set too high). Based on the consensus described above,[2] it should be measured on each particular jet separately. Afterwards, the areas of of all regurgitant jets should be added.

The 3D-guided planimetry of the vena contracta area is one of the most studied parameters in the assessment of MR after clip implantation not only because it is highly accurate and reproducible, but also because of its low interobserver variability.[21,23] Although this parameter was not used in the early studies,[14] nowadays it has become more popular. That is because it outlines the orifice better, lacks geometric assumptions, and has none of the artifacts produced by other measurements (figure 6).[24] It is often used because the most solid parameter to assess native MR is the regurgitant orifice area.[19] Several studies have confirmed that the 3D-guided TEE direct planimetry is the most reproducible and accurate imaging modality to estimate it.[6,13,23]

Hyodo, et al.[25] studied whether the 3D measurement of multiple vena contracta areas would be accurate enough to assess the severity of native valve MR. Until then, its utility was only known in single regurgitant jets. However, this was the first study to publish the results with multiple jets. Although this study has a small sample (n = 60), it proved that there is a high correlation between the 3D area and the ROA measured by thermodilution as the standard of use. This correlation was even more obvious in moderate or severe regurgitant jets, but it was overestimated in case of mild jets. After it was implemented on the native valve MR, its utility was assessed in patients with mitral clip. Avenatti et al.[13] conducted a retrospective study of 155 patients on this issue. The areas of multiple jets were added, and the results obtained between the local echocardiography lab and the echocardiography experts from 2 high-volume centers were compared. In the receiver operating characteristic (ROC) curves, a threshold of 0.27cm^2 was determined to identify moderate or more severe MR with an area under the curve of 0.81, and a negative predictive value of 92%. Although limited, their results are consistent with those from other registries and observational studies conducted in expert centers[14,26] that advocate for the use of this new measurement. Still, validation studies are needed to this point. However, we should be cautious regarding the addition of different areas of several jets since only the 2 studies mentioned above with a total of 215 patients have been been published to this date.

Finally, Altiok, et al.[6] shed more light on the utility of the vena contracta area measured on the 3D-guided echocardiography in residual MR. The regurgitant orifice areas measurements of residual MR obtained on the 2D transthoracic echocardiography (through the PISA) with 3D TEE (planimetry of the vena contracta area) were compared in 39 patients. In their results, interobserver variability was higher in 2D compared to 3D, which confirms the accuracy of the direct visualization of the regurgitant orifice compared to indirect measurements through the PISA that underestimate severity. Therefore, although it was not a 3D-guided validation study of the vena contracta, we can conclude that direct measurements of the vena contracta area through 3D TEE are reproducible and feasible in this population (figure 7 and figure 8).[13]

In conclusion, the 3D TEE of the vena contracta area is a promising parameter. As a matter of fact, it is the only one that would allow adding several jets.[12] However, it is in its infancy and more evidence would be required to this point. It is an arduous method that requires software analysis and is subject to blooming artifacts that can overestimate the area. Also, if the regurgitant orifice area is measured with color, such measurement is affected by both the temporal resolution and configuration of the aliasing velocity (signal saturation) that is not standard in the different softwares available.[12] In practice, these limitations complicate its application, which is why it is not the go-to parameter. Its utility can be greater in case of eccentric jets[27] because in these jets there is usually an initial asymmetry between the leaflets, which is why the residual jet can be eccentric even though a clip may be properly implanted. The 3D-guided direct planimetry should be more precise like the study conducted by Utsonomiya et al. suggests.[27] However, there is no more literature available on this regard.

Pulmonary venous flow pattern

This parameter is especially important given the assessment limitations of MR inside the valve. In case of severe regurgitation (3/4 or 4/4), the pulmonary systolic flow is totally or partially reversed in 1 or more pulmonary veins[19,28] with respect to an increased pressure towards the left atrium (figure 9).[29]

Similarly, its potential as a prognostic variable has been studied too. Ikenaga, et al.[28] measured the systolic velocity-time integral (VTI)/diastolic VTI ratio in the left upper pulmonary vein (unless

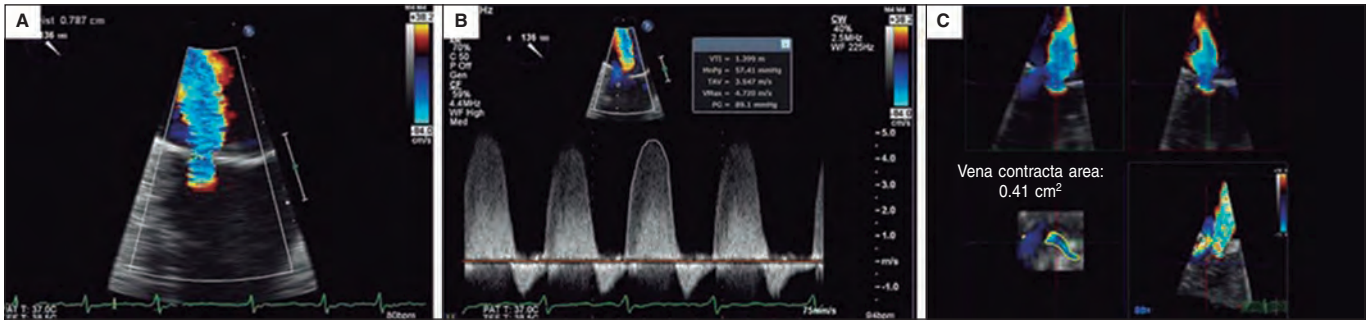

Figure 6. Two-dimensional transesophageal echocardiography image. **A** and **B** give an estimate of the effective regurgitant orifice area based on the proximal isovelocity surface area with a result of 0.32cm^2. Two-dimensional estimate of the proximal isovelocity surface area: effective regurgitant orifice area = 2π*r2 *aliasing velocity/mitral regurgitation peak velocity = [6.28 × (0.79) 2 *38.2]/472 = 150/472 = 0.32cm^2. **C:** when the measurement is taken using the 3D-guided direct planimetry, the result is 0.41cm^2. The 3D-guided direct planimetry gives more accurate measurements of the orifice because it eliminates the artifacts caused by indirect measurements. Reproduced with permission from Katz et al.[24].

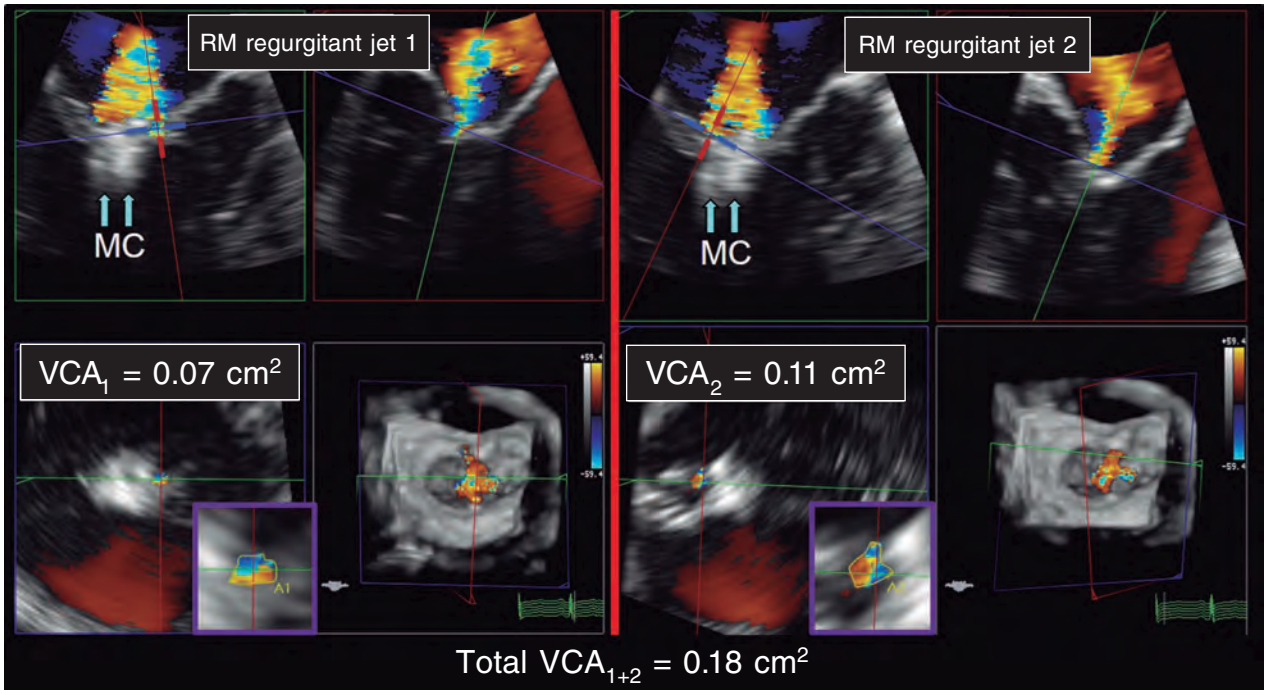

Figure 7. Two- and three-dimensional transesophageal echocardiography images. **A:** first mitral regurgitation jet (MR jet 1) after clip implantation (arrows, MC). **B:** second mitral regurgitation jet (MR jet 2) after clip implantation (arrows, MC). **C:** 3D-guided vena contracta area (VCA$_1$) estimate of the first jet with a result of 0.07 cm^2. **D:** 3D-guided vena contracta area (VCA$_2$) estimate of the second jet with a result of 0.11 cm^2. The sum of the 3D-guided vena contracta areas (total VCA$_{1+2}$) is 0.18cm^2. MC, MitraClip; MR, mitral regurgitation. VCA, vena contracta area. Reproduced with permission from Avenatti et al.[13].

the right ones were visible and had more damage). Using the ROC curves, they established that a cut-off point of 0.72 had the best area under the curve (0.67) with a 61% sensitivity and a 73% specificity. Therefore, ratios < 0.72 were associated with more major adverse cardiovascular events (adjusted hazard ratio [HR] of 1.26; 95% confidence interval [95%CI], 1.01-1.54; P = .047). Since the pulmonary flow curve can be difficult to obtain, the same estimates were made with the peak systolic velocity/peak diastolic velocity ratio, that proved that the cut-off ratio with the best area under the curve (0.62) was 0.83. This parameter was also significantly associated with major adverse cardiovascular events at the 12-month follow-up (adjusted HR, 3. 05; 95%CI, 1.53-6.30; P = .002). Since pulmonary venous flow is associated with left atrial pressure,[30] when MR drops, left atrial pressure decreases, and the pulmonary venous systolic component increases. When a new ROC curve was drew the peak systolic velocity/peak diastolic velocity ratio > 1.09 predicted left atrial pressures ≤ 12 mmHg (normal), a 71% sensitivity, and a 62% specificity. Peak systolic velocity/peak diastolic velocity ratios < 0.98 predicted left atrial pressures ≥ 20 mmHg, a 77% sensitivity, and a 71% specificity (figure 10 and figure 11).[28] However, there are some limitations to this[5,28] because, in case of atrial fibrillation, systolic flow is reduced following the loss of atrial contraction and relaxation. Also, in elderly patients, the rigidity of the atrium increases, and the systolic flow/diastolic flow ratio is lower. No standard cut-off values have been established and sometimes it is impossible to take any measurements due to the direction of the jet: for example, eccentric jets affect every pair of pulmonary veins differently causing artifacts that can impair the assessment of MR. The studies assessing pulmonary venous flow[28] always compare the same pulmonary vein at baseline

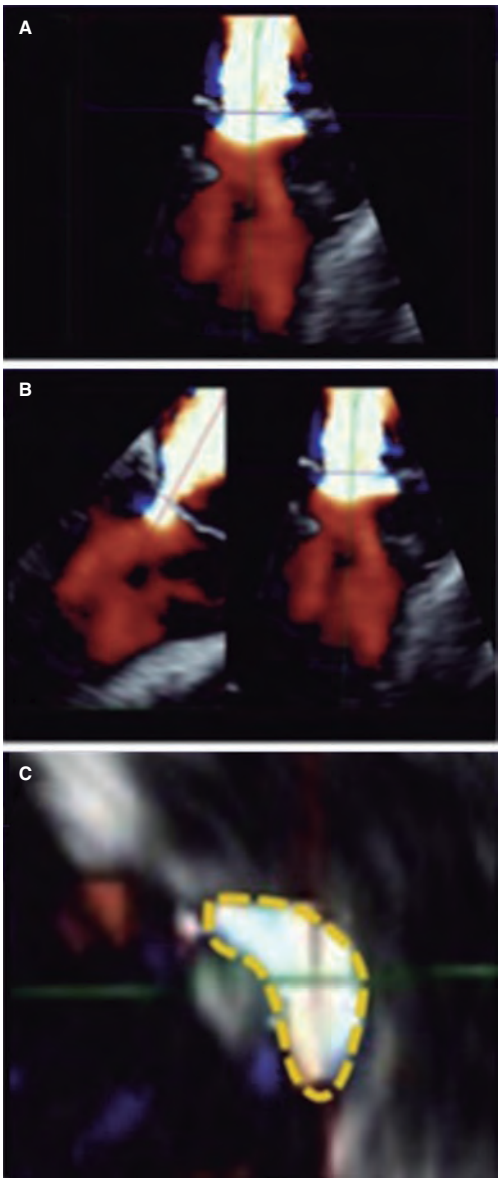

Figure 8. Two-dimensional transesophageal echocardiography image for the assessment of the vena contracta area. **A:** 3D color Doppler echocardiography of residual mitral regurgitation after clip implantation. **B:** axis alignment to obtain the 3D-guided vena contracta area. **C:** 3D-guided planimetry sketch. Reproduced with permission from Avenatti et al.[13].

and after clip implantation. There are still very few studies on this matter. However, in combination with other parameters, it can be part of a comprehensive assessment strategy before and after clip implantation (figure 12 and figure 13).[24,31]

Continuous-wave Doppler regurgitant jet

In native valve MR, the continuous-wave Doppler regurgitant jet can serve as an orientation. However, it is not sensitive enough to be used in isolation or to guide treatment.[19] Similarly, in case of clip implantation, the greater the density of the color Doppler signal, the higher the chances of severity although in the presence of multiple jets, it cannot be assessed properly[2] (figure 14).[30] No studies on its utility have been conducted to this date.

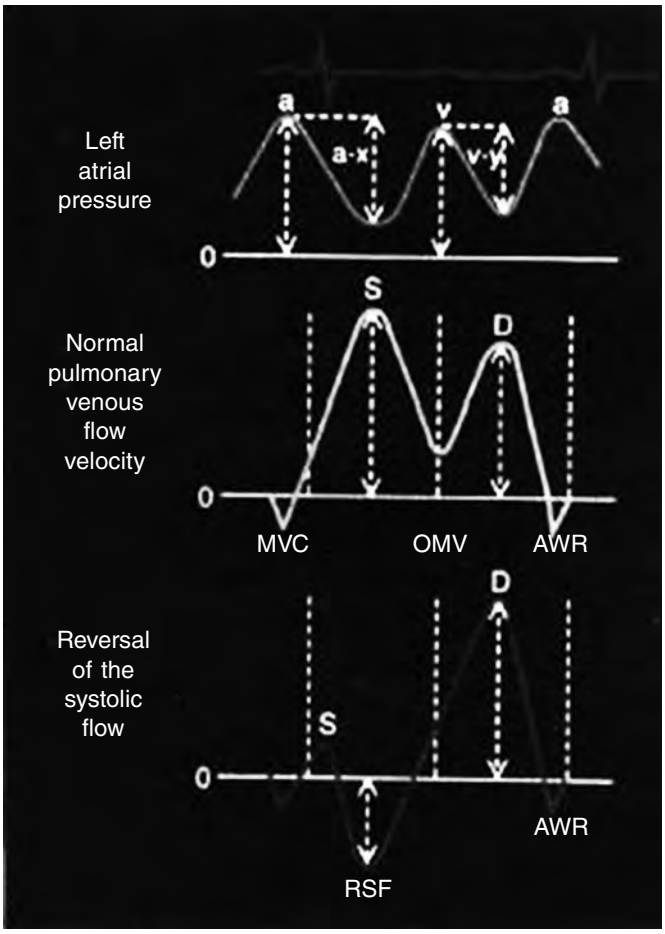

Figure 9. Scheme of atrial pressure waves and pulmonary flow. Up: left atrial pressure with the corresponding waves. Middle: normal pulmonary venous flow with a systolic wave > diastolic wave. Down: pulmonary venous flow with reversal of the systolic wave in the presence of severe mitral regurgitation. AWR, atrial wave reversal. MVC, mitral valve closure. OMV, opened mitral valve. RSF, reversal of the systolic flow. Reproduced with permission from Klein et al.[29].

Transmitral flow pattern by Doppler echocardiography

Slower E wave velocities are indicative of lower severities of native MR without quantifying it.[2] It cannot be used to estimate residual MR after clip implantation because the approximation of the borders of the mitral leaflets generates higher transmitral gradients.[30] Therefore, higher velocities are not indicative of significant residual MR.

Left atrial pressure with appearance of spontaneous contrast

The reduced volume of MR leads to atrial stasis (figure 15).[32] It can be indicative of lower severity in the presence of spontaneous contrast.[2] However, no studies have been conducted to this date.

Increased stroke volume in the left ventricular outflow tract

Same as before, an increased stroke volume can be indicative of reduced regurgitation. Still, the correlation between the left ventricular stroke volume and the severity of MR has not been studied, although we know that when it improves, MR often becomes attenuated.[2]

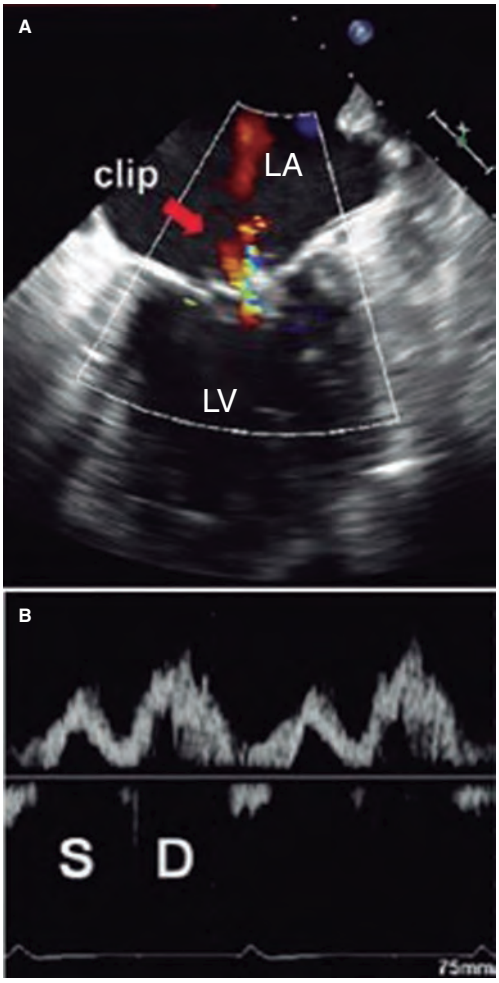

Figure 10. Two-dimensional transesophageal echocardiography image. **A:** color Doppler of residual mitral regurgitation after clip implantation (arrow). **B:** the corresponding blood flow at left upper pulmonary vein level is exposed with systolic (S) wave attenuation with respect to the diastolic (D) wave. The systolic velocity-time integral is 7.5 cm, and the diastolic one, 14 cm. The ratio between the 2 is 0.54, indicative of a higher risk of major adverse cardiovascular events. In this case, clip implantation is suboptimal. LA, left atrium, LV, left ventricle. Reproduced with permission from Ikenaga et al.[28].

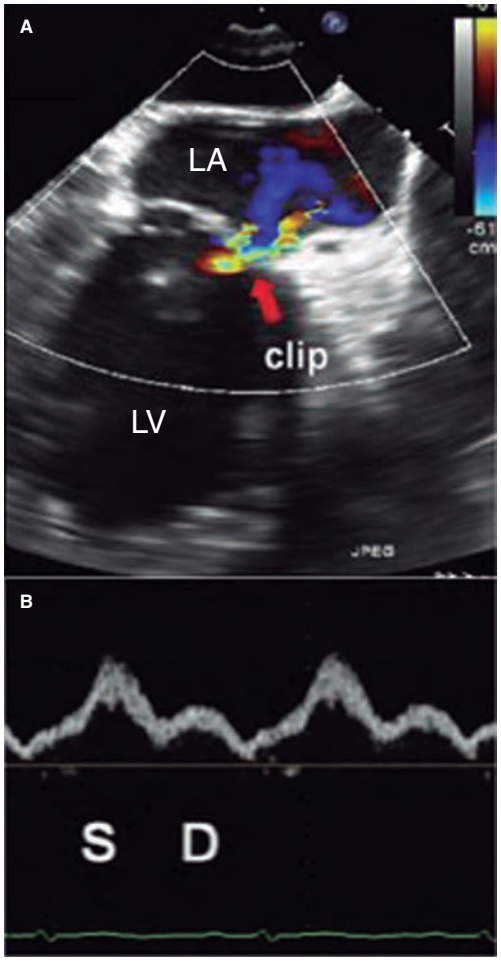

Figure 11. Two-dimensional transesophageal echocardiography image. **A:** color Doppler of residual mitral regurgitation after clip implantation (arrow). **B:** blood flow at left upper pulmonary vein level with a systolic wave (S) bigger than the diastolic (D) one. The systolic velocity-time integral was 23 cm, and the diastolic one, 10 cm with a ratio of 2.3, which is consistent with an optimal result at the follow-up. LA, left atrium. LV, left ventricle. Reproduced with permission from Ikenaga et al.[28].

Estimating the regurgitant volume

It has not been validated in this context[2] or in the multiple jet setting.

DISCUSSION

Residual MR after clip implantation conditions the patient's prognosis. Whether moderate or severe, the 12-month mortality rate can be twice as high as that of patients with mild MR.[13] Residual MR > moderate means persistent early clinical signs, and an increased left ventricular volume and cardiac remodeling. Similarly, if the severity of MR is not properly assessed intraoperatively, the number of clips required cannot be figured out. With too many clips, the risk of residual mitral stenosis is higher thus leading to worse prognosis.

The main limitation of the different studies conducted is that the standard of use is the assessment made by an expert operator. No single tool has proven capable of assessing MR easily, reproducibly, and regardless of the operator, which is why no validation studies can be conducted. Another limitation is that measurements taken under general anesthesia cause vasodilation, reduced ventricular

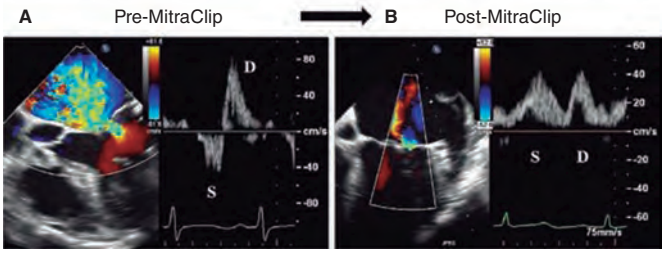

Figure 12. Two-dimensional transesophageal echocardiography image. **A:** color Doppler of severe mitral regurgitation (before mitral clip implantation) with pulmonary venous flow pattern. Reversal of the systolic (S) wave. **B:** presence of mitral regurgitation after clip implantation with corrected pulmonary venous flow pattern (systolic [S] wave > diastolic [D] wave). Reproduced with permission from Ikenaga et al.[31].

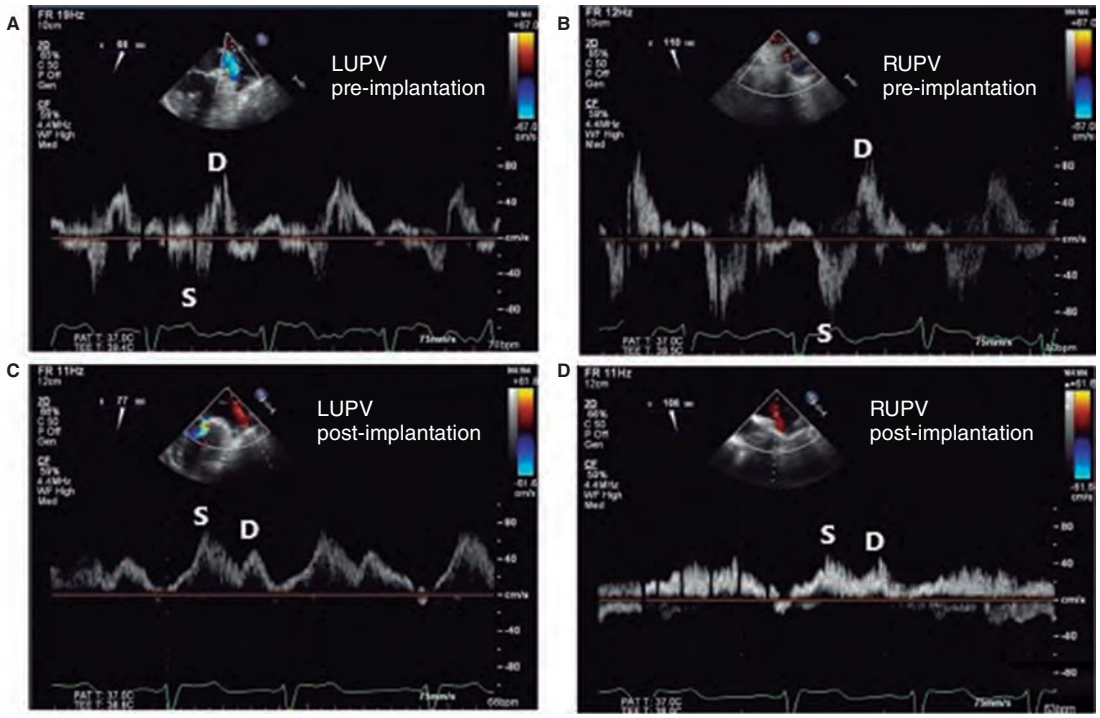

Figure 13. Images of pulmonary venous flow. **A:** blood flow at left upper pulmonary vein (LUPV) level before clip implantation with reversal of the systolic (S) wave with respect to the diastolic (D) wave. **B:** blood flow at right upper pulmonary vein (RUPV) flow level before clip implantation with reversal of systolic (S) wave with respect to the diastolic (D) one. **C:** blood flow at LUPV level after clip implantation with a systolic (S) wave bigger than the diastolic (D) one. **D:** blood flow at RUPV level after clip implantation with a systolic (S) wave bigger than the diastolic (D) one. Reproduced with permission from Katz et al.[24].

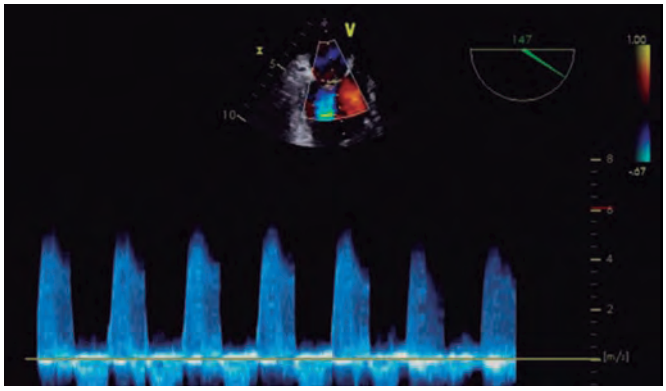

Figure 14. Transesophageal echocardiography image. Doppler image of a severe mitral regurgitation single jet. Its shape is triangular and density is high, suggestive of severity. Reproduced with permission from López-Opitz, and Moreno-Urrutia.[30]

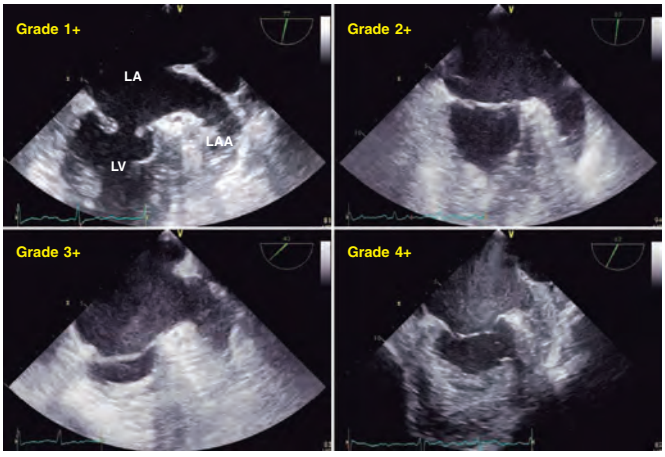

Figure 15. Two-dimensional transesophageal echocardiography image. A total of 4 different grades of spontaneous contrast can be seen in the atrium and the left atrial appendage going from lower to higher intensity (1+ to 4+). LA, left atrium; LAA, left atrial appendage; LV, left ventricle. Reproduced with permission from Ito and Suwa.[32]

afterload, and decreased MR. However, some studies published[13,23] show reproducible results up to 4 weeks after the procedure, basically with the 3D-guided vena contracta area. Intraoperative assessment under general anesthesia has not proven to underestimate the severity of residual regurgitation at the follow-up.

More and more studies focus on the 3D-guided vena contracta area or in the pulmonary venous flow. Although with limitations, the results obtained are both reproducible and consistent. The 3D-guided vena contracta area seems to be more precise since the 3D planimetry assessment is direct. However, it is an arduous method regarding its applicability in the clinical practice. Hoping that this will change in the future, several working groups focus on the 3D-guided vena contracta area thanks to its scarce interobserver variability and its good correlation with the severity of MR measured by expert operators.

Pulmonary venous flow has been gaining interest lately because it translates the left atrial pressure that is determined by the severity of MR (although age and atrial rhythm also play a role). Even so, when flow is compared before and after the procedure, the difference is attributed to the effect of the clip. However, in the native valve MR, it is a highly specific, though not very sensitive,

parameter. This can be extrapolated to residual regurgitation after device implantation.

CONCLUSIONS

The correct assessment of residual MR after mitral clip implantation has prognostic implications. However, the parameters used in native MR cannot be extrapolated because the clip causes a series of artifacts and morphological changes in the valve. Although some of these parameters (color Doppler echocardiography, transmitral flow, regurgitant volume, etc.) have not proven useful, others are promising. Both the 3D-guided vena contracta area and the pulmonary venous flow pattern are the 2 most promising parameters especially for their association with prognosis at the follow-up. Still, no validation studies have been conducted to this date. Standardizing software in all the centers and making 3D TEE available will be essential to further progress in the study of this valvular heart disease.

Residual MR after clip implantation has some peculiarities that make it ineligible to be assessed with the same parameters and values used with native MR. In practice, a comprehensive and efficient strategy is advised using the VCW and the variation of pulmonary venous flow plus, if possible, the 3D-guided vena contracta area.

Due to the rapid advance of this technique, updated manuscripts including data are required to be able to access the medical literature available. They should also include the prognostic significance of residual MR and encourage studies with enough scientific quality so that parameter validation studies can be conducted in the future. Also, so that the strategies used for residual MR assessment after mitral clip implantation can be standardized.

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AUTHORS' CONTRIBUTIONS

S.P. Cabrera Huerta conducted the bibliographic search, selected the articles of interest, and wrote the content of this manuscript. J.A. de Agustín directed the study and its content, verified the bibliographic sources, and reviewed all the searches.

CONFLICTS OF INTEREST

None.

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Debate: Ischemia without obstructive coronary artery disease. An invasive coronary physiological macro- and microvascular assessment is necessary

A debate: Isquemia sin enfermedad coronaria obstructiva. Es necesario un estudio invasivo fisiológico macro- y microvascular

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Question: Could tell us what the prevalence of angina without obstructive coronary artery disease is in patients referred for invasive angiography and how has it evolved over the last few years?

Answer: Nearly half of the patients referred for cardiac catheterization due to suspected stable angina have coronary arteries without obstructive lesions.[1] These numbers are even higher in the series of patients studied through cardiac computed tomography to the point that up to 3 out of 4 patients do not show any obstructive lesions. Women have a higher prevalence compared to men of up to 70%. Therefore, angina without obstructive lesions should not be considered a secondary problem, but a fundamental aspect of our routine clinical practice at the cath lab. Also, these patients have high rates of recurring angina and disability,[2] which means that achieving the proper diagnosis and administering the right treatment is of paramount importance.

Q.: We have been using the expression «without obstructive coronary artery disease», but it can be put into context. Shouldn't we rather say «without angiographically significant stenoses». Do you think that the physiological significance of stenoses with guidewire pressure should always be excluded, even the mild ones?

A.: With the evidence available, I believe that the systematic use of guidewire pressures to assess mild epicardial lesions is not justified. As a matter of fact, the correlation and concordance between angiography and fractional flow reserve (FFR) are modest, which is especially important in 50% to 90% stenoses where the angiography often overestimates functional severity systematically with rates of false positives > 50%.[3] On the other side of the spectrum, stenotic lesions < 50% on the angiography have a relatively low risk of being ischemic on the FFR and are almost anecdotal if < 30%. In a study conducted with 139 patients with angina and without obstructive lesions, the frequency rate of lesions with FFR ≤ 0.8 was 5%.[4] On the other hand, we should mention that the cut-off value validated to tag a coronary lesion as ischemic is 0.75 although, in practice, 0.8 is used to decide on whether to revascularize or not.

Regarding the clinical benefit of this approach, the large clinical trials that have proven the utility of FFR have only studied lesions > 50%, which is why we don't have data supporting the clinical utility of assessing mild lesions.[5,6] The RIPCORD-2 trial[7] presented in the Congress held by the European Society of Cardiology back in September 2021 included patients with, at least, 1 stenotic lesion ≥ 30%. All these patients' vessels were studied using the FFR and no clinical benefit was found. What this means is that probably the greatest benefit of FFR is to avoid unnecessary revascularizations, and to clarify the significance of truly suspicious lesions.

In practice, I think that the best thing to do is to individualize the decision-making process considering the angiographic severity, location of the lesion, and quality of angiographic assessment. A 20% lesion in a diagonal branch and a 40% lesion in the proximal left anterior descending coronary artery are 2 completely different things. Also, a focal lesion in a well-studied segment does not cast the same doubts as a long and calcified disease where a good angiographic assessment is not an easy thing to do due to curves, shortening, etc. Finally, we should remember that if a decision is made to measure microvascular function using a flow-pressure guidewire, the FFR can be established, almost at the same time, on suspicious lesions.

Q.: Once the significant stenosis of the epicardial vessel has been excluded, what should be the assessment protocol inside the cath lab?

A.: The invasive assessment of ischemia without obstructive lesions rests on 2 pillars mainly: the study of microcirculation, and the study of vascular reactivity.

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The study of microcirculation consists of assessing coronary flow at rest and during maximum hyperemia. To this end, pressure and flow guidewires, whether thermodilution-based (PressureWire, Abbott, United States) or Doppler-based (Combowire, Philips, The Netherlands) are used. Baselines measures are taken, then maximum hyperemia is induced with adenosine to eventually take the same measures once again. This allows us to estimate the coronary flow reserve that is the ratio between hyperemic and baseline flow (which should be > 2). Coronary flow reserve < 2 means that, in situations of exercise or other stressors, the patient cannot duplicate his oxygen supply to the myocardium eventually, thus leading to ischemia easily. Added to flow coronary reserve, the combination of pressure and hyperemic flow, can also estimate microvascular resistance. The most widely used measure is the microvascular resistance index (considered pathological if > 25.)[8]

The second part is to assess vasoreactivity since coronary arteries do not necessarily respond to physiological stimuli the same way they do to adenosine. As a matter of fact, coronary flow and vascular tone both of epicardial artery and microcirculation largely depend on the production of nitric oxide by the endothelium. If this production does not properly work, paradoxical vasoconstriction can be seen in physiological situations that would require hyperemia. That is why it is important to assess coronary reactivity, preferably using the acetylcholine provocation testing. It allows us to discard the presence of vasospastic angina, and endothelial dysfunction. We have recently published an article on *REC: Interventional Cardiology* with a detailed description on how to run and then interpret an acetylcholine provocation testing.[9]

This approach based on microvascular function and on the acetylcholine provocation testing has been backed by a group of experts from the European Society of Cardiology.[8] Regarding the logistics of the procedure, each lab should assess, depending on time availability, resources, and experience whether to perform the procedure *ad hoc* or whether to stage it, and arrange the order in which the tests will be run. We should bear in mind that, although the assessment of microcirculation requires the previous administration of nitroglycerin, the acetylcholine provocation testing requires just the opposite. Therefore, a possibility is to perform the angiography without nitroglycerin first, then the acetylcholine provocation testing, and finally measure the microvascular function. If nitroglycerin has been administered to achieve the diagnosis, the best thing to do is to measure the microvascular function next and leave the acetylcholine provocation testing for the end.

Q.: Is it possible to draw therapeutic implications from the comprehensive assessment of micro- and macrovascular coronary physiology?

A.: The main problem with microvascular and endothelial dysfunction is that no large clinical trial has ever confirmed any benefits regarding adverse events with any drugs. However, this should not take us to therapeutic nihilism because some former studies have proven the utility of different drugs reducing symptoms and improving quality of life.

If the patient is diagnosed with microvascular dysfunction, the first-line therapy here is beta-blockers. As coadjuvant or alternative therapy ivabradine, ranolazine, nicorandil, and calcium channel blockers can be used; nitroglycerin is not very useful here because it has a minor effect on microcirculation. Statins, and renin-angiotensin system inhibitors are advised too for the primary prevention of events.

If endothelial dysfunction-induced vasoconstriction or vasospastic angina are predominant, beta-blockers are ill-advised since they can make things worse. In this case, the first-line therapy is calcium channel blockers, nitrates, and nicorandil. The use of statins, and renin-angiotensin system inhibitors can be considered here too.

Empirical treatment has often been advised as an easier approach compared to physiological diagnosis and targeted therapy. Once again, each center should adapt its own clinical practice to its own possibilities. However, my own experience is that when these patients are not properly studied, they are not committed to the frequent visits that a careful empirical treatment would require; on the contrary, they are often discharged from the hospital and assessed at the 1-year follow-up, preventing us from conducting a proper follow-up of the symptoms and the effectiveness of treatment. On the other hand, considering that based on the physiological problem, there are very little effective treatments (like nitrates in microvascular dysfunction), and others are harmful (like beta-blockers in vasospasm), I think empirical treatment confront us with true dilemmas when treating patients who are not doing well.

Q.: What is the clinical evidence behind the invasive comprehensive assessment of coronary circulation? Have some advantages been identified regarding prognosis?

A.: Numerous studies from the 90s have proven that physiological disorders in patients with angina and without obstructive lesions are directly associated with myocardial ischemia and with long-term prognosis, as well as with the presence of atheromatous plaques and vulnerability data from intravascular imaging modalities. This is important because it is wrong to assume that all patients with angina and without lesions have the same disease and the same benign prognosis. Truth is that patients with endothelial and microvascular dysfunction have a far worse prognosis compared to patients with normal studies. Also, small trials have allowed us to establish the efficacy of different drugs based on the type of physiological dysfunction, as we have already discussed, thus supporting targeted therapy.

Regarding the prognostic benefit of individualized therapy, the CorMicA trial proved that this approach is superior to empirical treatment offering a better quality of life after 6 and 12 months.[10] To this date, we are still lacking studies with large enough samples to detect benefits regarding the adverse events. The iCorMicA trial (clinicaltrials.gov. Identifier: NCT04674449), currently ongoing, will be recruiting 1500 patients to study the benefits in quality of life and adverse events. In any case, with the results of the ISCHEMIA trial in mind,[11] I believe that only focusing on reducing hard events is a mistake that can prevent patients from receiving therapies that do help from the symptomatic and functional standpoint. In conclusion, I think there are enough scientific data to say that patients with angina and without obstructive lesions benefit from knowing their physiology and receiving individualized therapies.

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CONFLICTS OF INTEREST

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Debate: Ischemia without obstructive coronary artery disease. A non-invasive assessment may be sufficient in some cases

A debate: Isquemia sin enfermedad coronaria obstructiva. La valoración no invasiva puede ser suficiente en algunos casos

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Question: Is there a specific profile of patients with angina and without obstructive coronary artery disease?

Answer: Although we have been paying more attention to angina without obstructive coronary artery disease over the last few years (a more truthful denomination compared to ischemia with normal coronary arteries because it focuses on the clinical problem and also because many patients don't have strictly normal coronary arteries) we still don't know much about this syndrome. Syndrome X was the term coined back in 1973 after the group of patients with normal coronary arteries that was called group X.[1] Actually this term is more appropriate since this is the letter used in algebra to represent something that remains unknown.

Answering your question, it is more common in women; it is often exertional although a different kind of pattern has been reported too (first effort, at rest during certain hours, especially at night-time, exertional dyspnea); also, it is associated with known cardiovascular risk factors since most patients with angina and without obstructive coronary artery disease have coronary atherosclerosis.[2] Obesity, the association with inflammatory diseases (such as systemic lupus erythematous), mood swings, intolerance to different drugs are not rare, and make us have to try several combinations to control de symptoms.

Although it seems reasonable to suspect that a patient with angina may not have coronary artery lesions justifying the symptoms, these patients' profile is somehow similar to that of patients with clinically significant coronary artery lesions. Only an imaging modality capable of discarding clinically significant coronary artery disease can lead to a definitive diagnosis of angina without obstructive coronary artery disease.

Q.: The diagnosis of type of angina is, by definition, achieved after performing an invasive coronary angiography, but since the use of the computed tomography (CT) scan for coronary artery assessment has become more popular, can it also be diagnosed with a non-invasive angiography with a CT scan?

A.: To achieve the diagnosis of angina without obstructive coronary artery disease the following requirements need to be met:[3] *a)* compatible symptoms, *b)* lack of obstructive coronary artery disease, *c)* myocardial ischemia, and *d)* microvascular dysfunction. Therefore, if microvascular dysfunction is not confirmed, the diagnosis cannot be achieved. To answer this question properly we should ask ourselves a couple more questions first: can we diagnose microvascular dysfunction with non-invasive imaging modalities including the CT scan? also, can we achieve the diagnosis only with the clinical signs and proof that there is no obstructive coronary artery disease?

The diagnosis of microvascular dysfunction with non-invasive imaging modalities is feasible, although these are expensive or have been insufficiently validated. Positron emission tomography[4] and magnetic resonance imaging[5] have been able to confirm the presence of microvascular dysfunction in patients without macrovascular disease in different clinical settings. Contrast echocardiography[6] and Doppler echocardiography of the left anterior descending coronary artery[7] have also yielded favorable results in this context, but they are barely used.

Although it does not seem right to achieve the diagnosis without prior confirmation of microvascular dysfunction, it can be reasonable under certain circumstances. If the patient has typical symptoms and cardiovascular risk factors, treatment can be initiated

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after discarding obstructive coronary artery disease with a CT scan. If symptoms cannot be controlled, we can turn to the invasive study of microvascular function. This can be the go-to strategy in elderly or frail patients or with severe noncardiac diseases. It can even be used for the rest of patients since delaying symptom control does not compromise or worsen prognosis.

Q.: In the presence of mild or moderate stenoses on the CT scan, do you think that a non-invasive assessment of ischemia can help?

A.: Theoretically speaking, as I have already mentioned, we need confirmation of myocardial ischemia to achieve a definitive diagnosis of microvascular disease. There are situations, however, when we can assume the diagnosis if the patient shows typical symptoms and obstructive coronary artery disease has been discarded.

In patients with CT scans showing non-severe coronary artery lesions, we need to make sure that these lesions are not functionally significant before accepting the diagnosis of microvascular disease. The milder the lesion, the more certain we'll be that it is a non-functionally significant lesion, but microvascular dysfunction. Therefore, in moderate lesions, functional assessments are necessary to discard functionally significant disease. This assessment can be made while the CT scan is being performed by assessing coronary flow reserve[8] or with functional tests to see if there are traces of ischemia, and whether these traces originate at the diseased artery.

In any case, to me this question looks more like an academic issue than a practical one. If a patient has angina pectoris, a positive functional test for ischemia, a CT scan showing moderate disease of a coronary artery, and no left main coronary artery disease, medical therapy can be initiated, and the evolution of symptoms assessed. That is so because prognosis is not much better with an invasive approach as the ISCHEMIA trial proved.[9]

Q.: There are times when, depending on the center, the clinician can find himself with a symptomatic patient for angina who has been diagnosed with lack of coronary stenoses without even an invasive study of coronary physiology. What would the role of non-invasive imaging modalities be here?

A.: That is correct, a few years ago that was the rule of thumb: coronary artery disease was discarded, and there was no need to assess the vascular function. Currently, cardiologists are more aware of its importance, in part due to the interest shown by interventional cardiologists in this disease. Even so, we still see patients with angina pectoris in whom obstructive epicardial vessel disease has been discarded, but endothelium-related o non-related vascular dysfunction hasn't.

A positive ischemia assessment testing supports the diagnosis of microvascular dysfunction and, even in the absence of an invasive study of coronary physiology, it is good enough to initiate therapy. But if the patient does not get any better with the treatment suggested the invasive assessment of coronary physiology will be necessary to direct therapy towards the specific origin that's causing the coronary disorder.

Q.: What specific medical therapies are optimal based on the profile of coronary micro- and macrovascular pathophysiology?

A.: Evidence-based recommendations are very scarce. In the first place, cardiovascular risk factors should be put under control adequately, especially hypertension and diabetes mellitus, both of which contribute to vascular disease. Angiotensin-converting enzyme inhibitors and statins have proven effective to treat these patients. Controlling weight is essential, and a cardiac rehabilitation program can reduce symptoms and improve quality of life.

All types of antianginal drugs can be used in these patients, many times using a trial-and-error approach to it, because patients may be intolerant or drugs ineffective.

To choose the optimal drug therapy we should make a distinction between 2 different profiles of patients with angina pectoris without obstructive coronary artery disease: those with vasospastic angina pectoris and those with microvascular angina pectoris.

Patients with micro- or macrovascular spasm benefit from calcium channel blockers. Both dihydropyridine and non-dihydropyridine drugs can be effective, and the lack of effectiveness of one does not predict a lack of effectiveness of the other. Also, nitrates, both oral an in patches, can be used in this context.

In patients with microvascular angina pectoris not due to vasospasm, beta-blockers, calcium channel blockers, ranolazine, aminophylline, and trimetazidine have given effective results in preliminary trials, but not yet in randomized clinical trials. Although nitrates can be used in this type of patients, it has been proposed that symptoms could become worse.

Finally, antianginal drugs without significant hemodynamic effects can minimize symptoms in both groups of patients, especially ranolazine and trimetazidine.

Q.: With this therapeutic individualization, have any advantages been identified regarding prognosis?

A.: No beneficial effects have been confirmed regarding prognosis in mortality or myocardial infarction. However, fewer events of angina pectoris have been reported leading to a better quality of life, which is essential in these patients. The CorMicA trial[10] confirmed that an invasive study of coronary physiology in patients with chest pain and without obstructive coronary artery disease could identify 3 different groups (vasospastic angina pectoris, microvascular angina pectoris, and noncardiac chest pain). Also, that a specific medical strategy for each specific group reduced the occurrence of angina pectoris.

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CONFLICTS OF INTEREST

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Endovascular repair of the aortic arch with the NEXUS Stent Graft System

Reparación endovascular del arco aórtico con NEXUS Stent Graft System

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To the Editor,

Surgery of aortic arch diseases like aneurysms and dissections require invasive procedures that include cardiopulmonary bypass, selective cerebral perfusion, aortic cross-clamping, and hypothermic circulatory arrest.[1] Unfortunately, a large number of these patients are considered non-eligible for open surgical repair and receive medical therapy only.

The NEXUS Stent Graft System (Endospan Ltd., Israel) is indicated to treat high-risk surgical patients with ascending aorta and aortic arch diseases.[2] This device received European CE mark approval back in March 2019 for the endovascular repair of aortic arch disease including both aneurysms and dissections requiring landing in the zone 0. The NEXUS Stent Graft System is a dual module device that is inserted through a 20-Fr delivery system. The integrated brachiocephalic artery branch avoids the possibility of branch separation and the interlocking latch mechanism avoids the migration or separation of the modules. This article describes the implantation of a NEXUS branched aortic stent graft system in Spain for the first time. Patient's written informed consent for publication was obtained.

This is the case of a 75-years-old male patient with an enlarged downstream aorta 6 months after ascending aortic replacement with open distal anastomosis due to acute type A aortic dissection. The follow-up coronary computed tomography angiography performed revealed the presence of an enlarged aortic arch and descending aorta (from 4.1 mm to 5.2 mm). The patient was considered non-eligible for open surgical repair by the heart team and a decision was made to proceed with the endovascular management of the diseased segment of the aorta.

The patient underwent extra-anatomic reconstruction with right common carotid artery to left subclavian artery bypass (both end-to-side) and proximal ligation with an 8-mm polytetrafluoroethylene vascular graft and end-to-side reimplantation of the right common carotid artery on the graft. Six weeks later, the endovascular procedure was performed. The day prior to the procedure, cardiac pacing was used to induce hypotension during stent graft deployment. Under general anesthesia, the NEXUS Stent Graft System was inserted via right groin towards the ascending aorta. Intravenous heparin was infused (5000 IU) during the preparation prior to the insertion of the device and on the introduction of the NEXUS device main body module. More heparin was infused (300 IU/kg of the patient's body weight) to reach an activated clotting time > 300 seconds to 400 seconds. Added to percutaneous groin access (20-Fr sheath), 2 smaller access sites are required, 1 at opposite groin level (12-Fr sheath with 2 5-Fr angiographic catheters) and the other one at right brachial artery level (7-Fr sheath). The main module was introduced via right brachio-femoral access using the through-and-through wire technique (0.035 in x 450 cm, Hydra Jagwire, Boston Scientific, United States). The side-branch landed on the brachiocephalic artery covering both the aortic arch and the descending aorta (figure 1). Afterwards, through a guidewire (0.035 in x 300 cm, double curved Lunderquist Extra-Stiff Wire, Cook Medical, United States) placed in the left ventricle and during rapid pacing, the ascending aorta module was implanted. After aortic remodelling with a kissing balloon angioplasty (Reliant, Medtronic and 12 mm x 40 mm Armada 35 PTA, Abbott Vascular, United States), a thoracic stent graft was implanted 3 cm above the celiac trunk (E-vita thoracic, Jotec). The patient was discharged 6 days after the endovascular procedure on 75 mg/day of clopidogrel. The coronary computed tomography angiography performed at the 3-month follow-up confirmed the absence of endoleaks and false lumen thrombosis until the end of the implanted stent grafts (figure 2).

The NEXUS aortic arch stent graft system is indicated for the endovascular management of thoracic aortic diseases involving the aortic arch with proximal landing zone into the ascending aorta and the brachiocephalic artery.

Early experiences with the NEXUS arch graft have been successful. Lindsay et al.[3] published a prospective cohort of 5 patients treated with the NEXUS Stent Graft System. No periprocedural strokes occurred. However, postoperative imaging revealed the presence of an ascending aortic hematoma in 1 patient who required ascending aortic replacement. After a 1.5-month-to-13-month follow-up, no endoleaks or other complications were seen.

During 2019, the 2-year results if a prospective, multicenter, premarket study including 25 patients (mean age, 73 years) treated with the NEXUS Stent Graft System were presented.[4] Technical success was achieved in all the deployments (100%). At 30 days, 2 patients (8%) died of cardiac causes and another 2 (8%) experienced non-disabling stroke that resolved completely within 30 days. During a mean follow-up of 25-months, there was 1 additional procedure-related death due to stroke, and 1 patient crossed over to open surgery after a retrograde type A dissection.

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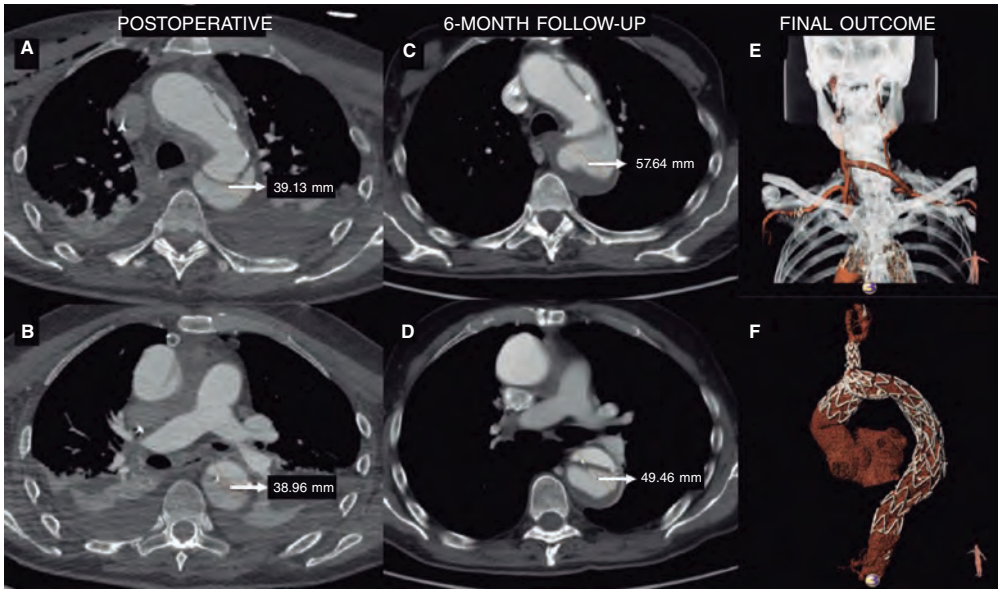

Figure 1. **A, B, C, D:** aortic enlargement after open ascending aorta replacement as seen on the coronary computed tomography angiogram performed at the 6-month follow-up. **E:** extra-anatomic reconstruction with right common carotid artery to left subclavian artery bypass (both end-to-side), proximal ligation, and end-to-side reimplantation of the right common carotid artery on the graft. **F:** ascending aorta open replacement, NEXUS Stent Graft System implantation into aortic arch and descending thoracic aorta with false lumen thrombosis.

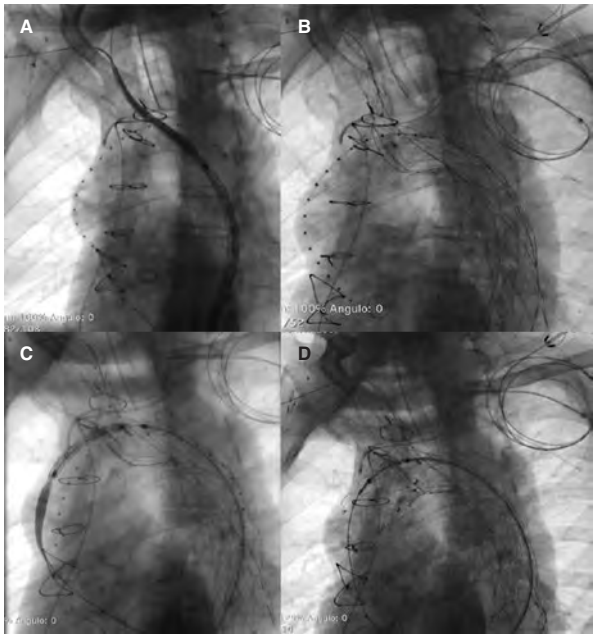

Figure 2. **A:** NEXUS Stent Graft main module position. **B:** NEXUS main module deployment. **C:** NEXUS ascending module positioning. **D:** NEXUS complete deployment.

The practical therapeutic implications include the management of aortic arch diseases like aneurysms and chronic dissections, especially in high-risk surgical patients. This device allows a minimally invasive procedure with no cardiopulmonary bypass, aortic cross-clamping, and circulatory arrest.

The NEXUS Stent Graft System represents the first branched endoprosthesis available off-the-shelf in Europe for the endovascular repair of the aortic arch, especially in high-risk patients with complex aortic arch diseases. It is a promising minimally invasive technique. Still, more experience on this regard and a longer follow-up are needed to confirm the promising mid-term results reported.

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AUTHORS' CONTRIBUTION

E.M. San Norberto, N. Cenizo and C. Vaquero performed the interventional procedure, C.M. Flota contributed to case preparation, E.M. San Norberto and C. Vaquero wrote the article in consultation with N. Cenizo and C.M. Flota. All authors provided critical feedback, and helped shape the research and analysis.

CONFLICTS OF INTEREST

None.

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New PASCAL Ace implant system in complex percutaneous mitral valve repair

Nuevo PASCAL Ace en la reparación percutánea valvular mitral compleja

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To the Editor,

We present the case of a 73-year-old woman with arterial hypertension, morbid obesity (122 kg, body mass index = 44), and chronic lower limb swelling with recurrent skin infections due to multidrug resistant microorganisms. She had a significant degenerative mitral regurgitation with moderate pulmonary hypertension and dyspnea, and NYHA functional class II. Despite the patients' low surgical risk scores (1.5% and 1.29% in the Society of Thoracic Surgeons and EuroSCORE II scales, respectively) she was considered noneligible for mitral surgery because of her obesity and perioperative infectious risk. The heart team studied the case and decided to treat the mitral regurgitation with percutaneous treatment whose overall risk is lower. The patient's informed consent was obtained for data publication in observance of the Declaration of Helsinki ethical principles.

While planning the procedure, the presence of degenerative mitral regurgitation was confirmed associated with chord rupture and posterior leaflet eversion (flail) of the P1 scallop (figure 1A,B, asterisks) of 9 mm in height and 14 mm of amplitude. Quantitative parameters suggested a 1.3 cm^2 anatomical regurgitant orifice, a 50 mL regurgitant volume, and a 51% regurgitant fraction with hemodynamic repercussion on the right superior pulmonary vein and systolic component reversal. The mitral valve apparatus was preserved with a 7.2 cm^2 area according to the 3D planimetry. However, the mean gradient was somehow higher (4 mmHg) probably due to the mitral regurgitation hyperflow and an increased cardiac output (estimated in 11 L/min) in atrial fibrillation at 125 beats per minute.

The defect was repaired using the PASCAL Ace device (Edwards Lifesciences, Irvine, CA, United States). This is a percutaneous mitral valve repair system to correct mitral regurgitation using the edge-to-edge technique via femoral vein and transseptal access to reach the left atrium. The PASCAL device is basically different from the MitraClip (Abbott Laboratories, Abbott Park, IL, United States) in that it has a central spacer to refill the regurgitant orifice and an elongation feature to remove it from the ventricle (at the eversion site) that makes it safer. The PASCAL Ace is a variant of the original design with a lower amplitude compared to the latter (6 mm vs 10 mm), and a smaller central spacer (2 mm vs 5 mm). The objective of these changes was to be able to treat more complex anatomies like our case. Due to the paracommissural anatomy, the original device could easily tangle up in the chordae of the subvalvular apparatus.

The procedure was performed under general anesthesia and continuous echocardiographic monitoring. Access to the left atrium occurred through a transeptal puncture 43 mm from the valvular plane. The clasping of the leaflets was attempted repeatedly for the complete correction of the anatomical defect. An independent clasping system was used to optimize the anterior and posterior leaflet grasping. In 1 of the attempts, the device got trapped into the subvalvular apparatus, but it could be easily retrieved thanks to the device elongation. The eversion was eventually immobilized (figure 1C) with an early clasping maneuver of both leaflets and significant optimization towards the posterior leaflet. This reduced mitral regurgitation significantly (figure 1D), improved the hemodynamic parameters, and returned the patient to a normal sinus rhythm. The final gradient was reduced down to 2 mmHg after the hemodynamic improvement with a final mitral area of 4.4 cm^2. Clinical evolution was favorable and without complications. The patient was discharged from the hospital 24 hours after the procedure and functional class improved slightly at the follow-up.

The percutaneous treatment of severe mitral regurgitation is well-established today.[1] There are different devices available in the market, although the edge-to-edge therapy that simulates the Alfieri surgical technique, basically with a MitraClip device, is the most popular one. Also, it is the one on which there is more evidence available to this date.[2-4] The PASCAL system[5,6] has several particular features: the central spacer, the independent clasping of the leaflets, and the possibility of elongating the device inside the ventricle for retrieval purposes. The central spacer seems to generate less tension inside the mitral valve, especially in mitral regurgitations of functional mechanism with significant tension. The independent grasping of the leaflets facilitates maneuvers to optimize the insertion of the leaflets securing a more stable fixation of these. However, to avoid small valvular distortions that may trigger unexpected final regurgitations, the first grasp is performed with a simultaneous reduction of the clasping followed by an independent clasping to optimize results. The possibility of elongating the device when trapped inside the subvalvular apparatus makes its retrieval much easier. The PASCAL Ace system is less voluminous, but it can increase the insertion of the leaflets up to 1 mm. This facilitates treating more complex anatomies when there is a risk of interfering significantly with neighboring structures. This was the very first experience in Spain with the PASCAL Ace system.

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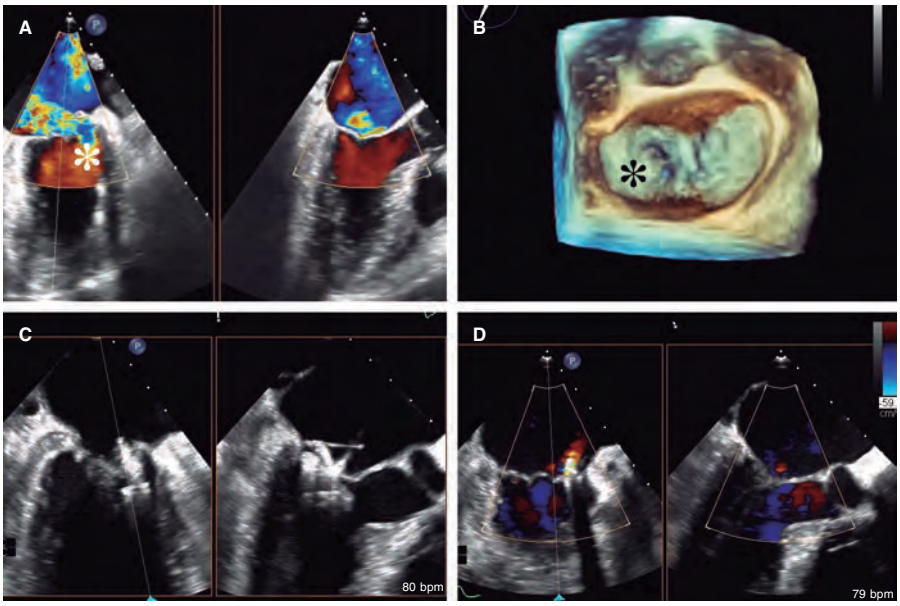

Figure 1. PASCAL Ace device implantation in a patient with complex mitral regurgitation. **A:** bi-plane color Doppler transesophageal echocardiography imaging. **B:** 3D reconstruction of the mitral valve showing the P1 eversion (asterisks) accompanied by a significant jet towards the septum. **C:** final clasping of the leaflets. **D:** very mild final regurgitant jet.

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AUTHORS' CONTRIBUTION

All the authors have contributed substantially to the concept, design, analysis, and interpretation of this manuscript. They also conducted a critical review of its intellectual content and approved it for publication. Finally, they take full responsibility on the truthfulness of this study.

CONFLICTS OF INTEREST

D. Arzamendi received personal fees from Edwards Lifesciences while conducting this study.

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The ReCross dual-lumen microcatheter versatility during percutaneous coronary intervention of chronic total coronary occlusions

Versatilidad del microcatéter ReCross durante la angioplastia de oclusiones coronarias crónicas

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To the Editor,

Microcatheters are essential tools to facilitate guidewire manipulation and exchange, thus enhancing the guidewire penetration force.[1] The ReCross over-the-wire dual-lumen microcatheter (DLM) (IMDS, The Netherlands) is the latest evolution among DLM microcatheters. However, no data are available in the medical literature yet. From September 2020 through November 2020 a total of 8 patients undergoing percutaneous coronary intervention (PCI) of chronic total coronary occlusions (CTO) with the ReCross at 5 Italian high-volume PCI-capable centers were retrospectively identified. This study complied with the Declaration of Helsinki, and written informed consent was obtained from all participants.

Case 1. A proximal right coronary artery CTO underwent antegrade approach using the ReCross microcatheter (IMDS, The Netherlands) as a first choice due to the presence of a bifurcation at distal cap level (figure 1A). The antegrade wire escalation technique was used with an Ultimate Bros 3 guidewire (Asahi Intecc, Japan) followed by a Gaia Second guidewire (Asahi Intecc, Japan) that was able to cross the CTO body and reach the side branch (right ventricular branch) distal true lumen (figure 1B). The ReCross was advanced over the Gaia Second guidewire through the lesion close to the bifurcation; afterwards, another Gaia Second guidewire was advanced through the blue lumen and easily directed towards the distal main vessel (figure 1C). The ReCross was then advanced as a single-lumen microcatheter (SLM) into the distal right coronary artery true lumen.

Case 2. The CTO of a mid-left anterior descending coronary artery (LAD) underwent antegrade approach with the ReCross as the single-lumen microcatheter using the antegrade wire escalation strategy. However, all the guidewires went subintimal and finally the successful recanalization of the occluded artery was achieved

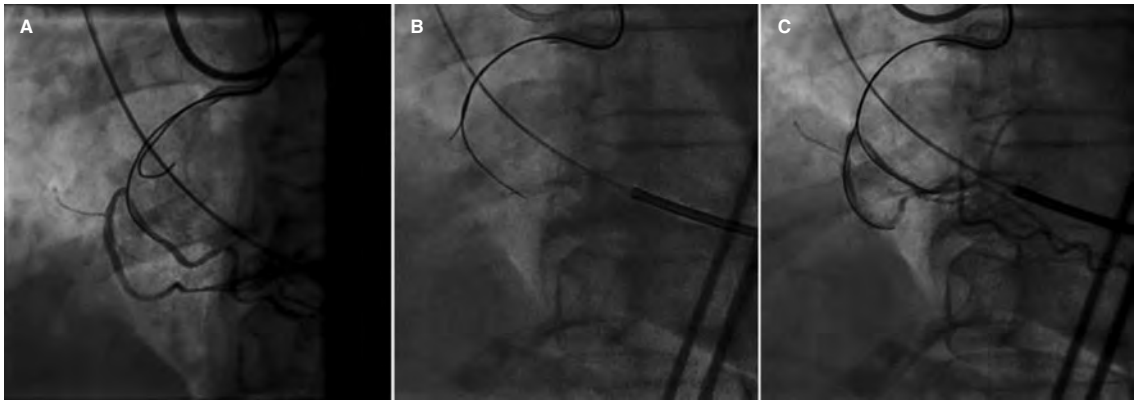

Figure 1. Bifurcation at distal cap level. **A:** the first chronic total coronary occlusion guidewire (Gaia Second) went into the side branch; **B:** a second chronic total coronary occlusion guidewire (Gaia Second) was inserted through the hub of the stylet lumen to engage the main vessel; **C:** a controlateral injection confirmed the correct positioning of the second guidewire into the main distal true lumen.

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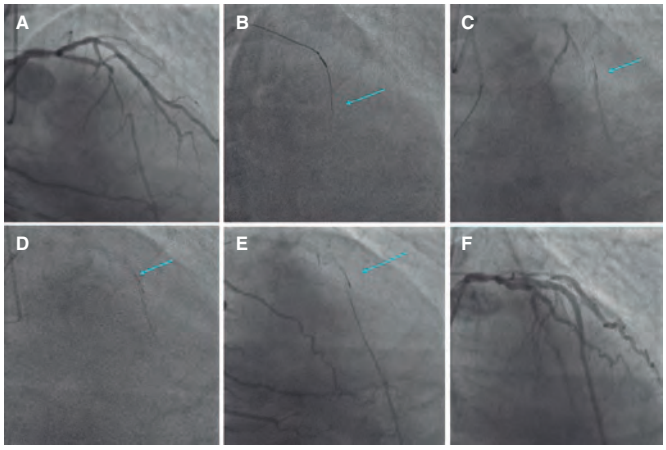

Figure 2. Antegrade dissection and re-entry. **A:** mid-left anterior descending coronary artery chronic total coronary occlusion; **B:** unintentional guidewire subintimal tracking (arrow); **C:** a retrograde superselective tip injection from the septal connection shows the subintimal tracking of the ReCross microcatheter (arrow); **D:** subintimal guidewire redirection with a stiff guidewire advanced through the stylet lumen to perform a controlled re-entry puncture from the subintimal space into the true lumen (arrow); **E:** the contralateral injection confirms the correct positioning of the second guidewire into the distal true lumen (arrow); **F:** final outcome after successful percutaneous coronary intervention of left anterior descending coronary artery chronic total coronary occlusion.

using an antegrade dissection and re-entry strategy (ADR). The ReCross microcatheter was advanced over the subintimal guidewire through the white lumen down towards the CTO (figure 2A). Then, a second stiffer guidewire was advanced through the blue lumen and redirected from the subintimal space (figure 2B) into the distal true lumen (figure 2C). The remaining cases are shown on table 1.

The ReCross microcatheter is the new member of the DLM family and its main technological advances are represented by *a)* the presence of an over-the-wire (OTW) system instead of a monorail system for the tip lumen; *b)* an additional exit port (the third one) in the tip lumen at a 180° angle of the exit port of the stylet lumen. The second OTW lumen gives the possibility of exchanging and using 2 different guidewires simultaneously and the additional exit port facilitates the redirection of the guidewire (figure 2). In the following paragraphs we detail the versatile use of the ReCross in different anatomical settings during the PCI of a CTO.

Combination of CTOs and bifurcations: the presence of bifurcation lesions in the context of a CTO can be one of the most complex subsets during the PCI.[2] In case of a bifurcation close to the proximal cap, the ReCross can be selected as a frontline microcatheter as the procedure is expected to require dual guidewire access. The ReCross is advanced over the workhorse guidewire inside the side branch until the proximal cap. Then, a CTO dedicated guidewire can be advanced through the second OTW lumen to negotiate the occlusion. This technique allows precise manipulations of the CTO guidewire and increases support to be able to penetrate the proximal cap.[3] Notably, when the use of intravascular ultrasound-guided puncture is required, the small profile of the ReCross allows the simultaneous use of both devices in a 7-Fr guiding catheter with a large lumen. After successful puncture of the proximal cap the ReCross microcatheter should be removed from the side branch using the trapping technique. Afterwards, it can be re-advanced as a SLM to support the guidewire advance into the distal target true lumen. Finally, when facing a bifurcation inside the CTO body like at distal cap level, the use of the ReCross can be essential for the CTO guidewires to engage the side branch. In this scenario, the ReCross can be advanced at bifurcation level and a second CTO guidewire can be inserted through the second OTW lumen to engage the main distal vessel (case 1).

Unintentional antegrade guidewire subintimal tracking: in many antegrade procedures when the first guidewire goes subintimal, the most useful strategy is to use the parallel guidewire technique. The first guidewire is left in place as a marker occluding the false lumen and modifying the anatomy of the vessel. The first microcatheter must be replaced by a DLM, which is advanced over the subintimal guidewire. Afterwards, a second dedicated CTO guidewire can be used to re-engage the cap for intentional intimal plaque tracking.

Table 1. Case series

	Artery involved	Approach	Technique used	Anatomical setting	J-CTO score	Fluoroscopy time (min)	Guidewires used	CTO recanalization
Case 1	RCA	Antegrade	DLM	Combination of CTO and bifurcation	2	35	UB3, Gaia Second	Yes
Case 2	LAD	Antegrade	ADR	Unintentional antegrade guidewire subintimal tracking	3	77	UB3, Gaia Second, Gaia Third, CP 12	Yes
Case 3	RCA	Antegrade	Parallel guidewire	Unintentional antegrade guidewire subintimal tracking	2	58	UB3, Gladius, Gaia Second	Yes
Case 4	RCA	Antegrade	ADR	Hematoma decompression	3	65	Gladius, Gaia Second, Gaia Third, Hornet 14	Yes
Case 5	LCX	Antegrade	Parallel guidewire	Unintentional antegrade guidewire subintimal tracking	3	73	UB3, Gaia Second, Gaia Third, CP 12, Hornet 14	Yes
Case 6	LAD	Antegrade	Parallel guidewire	Unintentional antegrade guidewire subintimal tracking	2	61	Gladius, Gaia Second	Yes
Case 7	RCA	Antegrade	DLM	Combination of CTO and bifurcation	2	46	Fielder XT-R, UB3	Yes
Case 8	RCA	Retrograde	DLM	Combination of CTO and bifurcation	3	88	UB3, Suoh 0.3, Gaia Second	Yes

ADR, antegrade dissection and re-entry; CTO, chronic total coronary occlusion; DLM, dual-lumen microcatheter; LAD, left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery.

In those cases in which the parallel guidewire technique is required, the ReCross microcatheter allows the insertion of a second CTO guidewire through the hub of the stylet lumen in order to re-engage the cap. By using the ReCross device operators can advance simultaneously 2 CTO guidewires through 2 different OTW lumens, somehow similar to the pioneering see-saw wiring technique with 2 SLMs.

Antegrade dissection and re-entry (ADR): ADR techniques are characterized by the intentional use of the subintimal space to cross coronary CTOs followed by the subsequent re-entry into the distal true lumen.[4] Several devices have been developed to facilitate a controlled ADR (CrossBoss microcatheter and the Stingray balloon; Boston Scientific, United States). The main limitations of these devices are their costs and crossing-profile, which often requires prior balloon dilatation with the corresponding increase of subintimal hematomas. Conversely, the ReCross microcatheter can be advanced into the subintimal space distally to the occlusion often without the need for vessel pre-dilatation to perform a subintimal guidewire redirection. The operator can advance a stiff guidewire through the appropriate lumen to perform a controlled re-entry puncture from the subintimal space towards the true lumen.

Additionally, with the ReCross device it is possible to use 2 CTO guidewires simultaneously to achieve re-entry from the subintimal space towards the true lumen with an high success rate. Moreover, the first lumen can be used for vessel decompression of the subintimal hematoma, thus facilitating the re-entry of the second guidewire. In conclusion, the ReCross device provides a versatile and attractive alternative to standard DLM when performing the PCI of a CTO potentially reducing procedural costs and time.

FUNDING

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AUTHORS' CONTRIBUTIONS

R. Garbo, M. Iannaccone, J. Sanz Sánchez, and G.L.Gasparini contributed to the design, analysis, and writing of this manuscript. J.A.Oreglia, and A.Gagnor contributed to the design, and writing of this manuscript too.

CONFLICTS OF INTEREST

None reported.

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Percutaneous edge-to-edge tricuspid valve repair in congenitally corrected transposition of the great arteries

Reparación percutánea borde a borde de la válvula tricúspide en transposición de grandes vasos congénitamente corregida

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To the Editor,

The congenitally corrected transposition of the great arteries is a rare congenital defect characterized by atrioventricular and ventriculoarterial discordance. As a result, the tricuspid valve and the anatomical right ventricle sustain the systemic circulation. Typically, the patient remains asymptomatic at an early age, but the right ventricle and the tricuspid valve deteriorate with the passing of time. The only curative treatment for this condition is heart transplant. In this setting, percutaneous edge-to-edge tricuspid valve repair has been traditionally used to treat tricuspid regurgitation in patients who are ineligible for heart transplantation; however, to this date, the evidence available is scarce and based on case reporting in heterogeneous clinical settings.[1-3]

This is the case of a young male patient with congenitally corrected transposition of the great arteries, advanced heart failure, and torrential tricuspid regurgitation considered ineligible for heart

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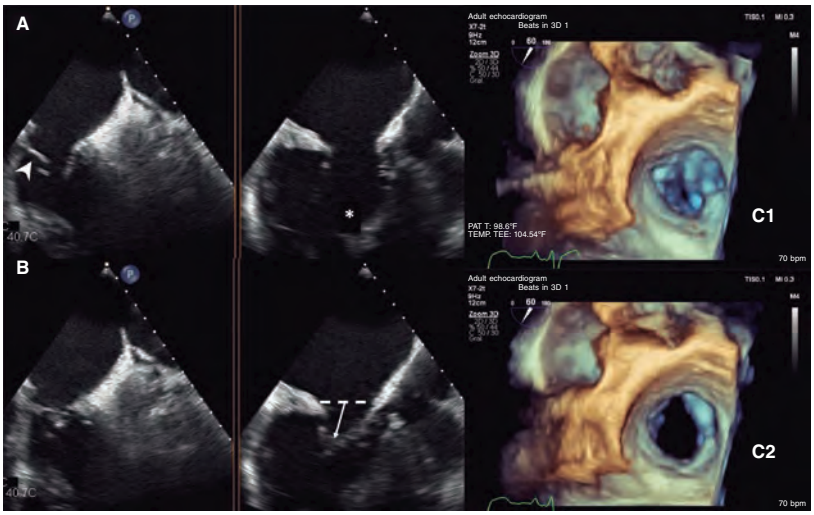

Figure 1. Detailed assessment of the anatomy of the tricuspid valve on a 2D and 3D transesophageal echocardiogram. X plane views in 55-degrees (left), and 145-degrees (middle) in end-diastole **(A)**, and end-systole **(B)**. Significantly dysplastic leaflets (arrowhead) with Ebstein-like apical displacement of the insertion, and anomalous chordae tendineae implantation (asterisk) causing tension and bulge (arrow). **C:** mitral valve assessment with 3D zoom showing a large coaptation gap predominantly between the septal and the posterior leaflets in end-systole (**C1**) and end-diastole (**C2**).

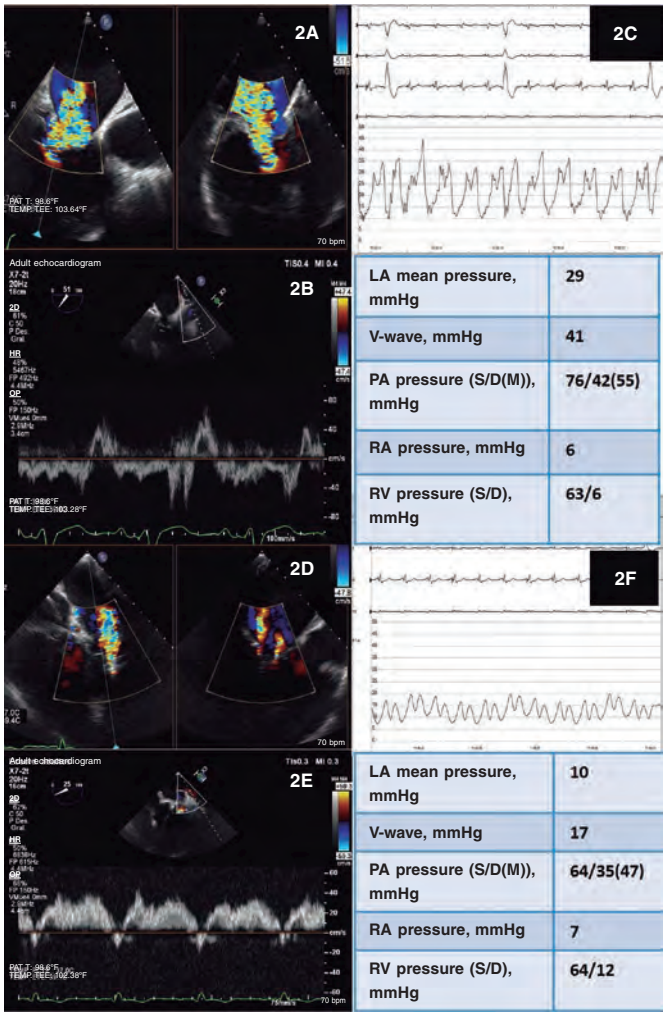

Figure 2. Tricuspid regurgitation before and after the procedure. **A, D:** bi-plane color TEE. **B, E:** pulsed wave Doppler ultrasound of the left superior pulmonary vein. **C, F:** traces and values of the invasive hemodynamic assessment. LA, left atrium; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

transplantation due to irreversible severe pulmonary hypertension, but eligible for percutaneous edge-to-edge tricuspid valve repair. The patient signed an informed consent form authorizing the publication of his case that was eventually approved by our center ethics committee.

This is the case of a male diagnosed with congenitally corrected transposition of the great arteries and congenital atrioventricular block at the early age of 7 months. The patient remained asymptomatic until he was 29 years-old when he required a pacemaker due to presence of chronotropic incompetence. Afterwards, he was lost to follow-up until he was admitted to the intensive care unit with signs of pulmonary edema at the age of 35 when he was diagnosed with biventricular systolic dysfunction, severe systemic atrioventricular valve regurgitation, and pulmonary hypertension. Due to the occurrence of a cardiac arrest, an implantable cardioverter-defibrillator with resynchronization therapy was indicated followed by the optimal medical therapy.

Despite treatment, the patient remained symptomatic with New York Heart Association functional class III, and INTERMACS 4. The echocardiographic assessment revealed the presence of severe systemic ventricular systolic dysfunction (right ventricular ejection fraction = 35%) with severe regurgitation of the systemic atrioventricular valve. The valve showed an Ebstein-like anomaly (8.3 mm/m^2), abnormal chordae structures, and thickened leaflets with restriction of motion causing a wide coaptation defect, mainly between the septal and posterior leaflets triggering torrential regurgitation (V/V) (figure 1). Cardiac catheterization revealed the presence of severe pulmonary hypertension (mean pulmonary artery pressure of 55 mmHg) with pre- and post-capillary components (transpulmonary gradient of 30 mmHg, and pulmonary vascular resistance of 6.4 WU). The vasodilator test with nitric oxide resulted in a maximum response, but without any significant changes. Considering all this information, the heart team decided that the patient remained ineligible for heart transplantation and suggested the percutaneous edge-to-edge tricuspid valve repair of the tricuspid valve with a MitraClip device (Abbott Vascular, United States) as palliative treatment.

During the procedure the presence of torrential tricuspid regurgitation was confirmed (figure 2A,B) with consistent invasive

hemodynamic findings (figure 2C). An early MitraClip XTR device was implanted at the origin of the regurgitant jet at the center of the septal-posterior coaptation line that was able to reduce regurgitation significantly. However, due to the presence of moderate-to-severe persistent regurgitation (II-III/V) without significant stenosis a second device had to be implanted between the anterior and septal valves for being the area with the greatest residual regurgitation. The outcome assessment confirmed the presence of mild-to-moderate residual tricuspid regurgitation (II/V) (figure 2D,E) without stenosis. This positive outcome was also confirmed on the invasive assessment (figure 2F), which is why the procedure was considered terminated.

Despite the slight worsening of tricuspid regurgitation at the 6-month follow-up (grade III/V), and the presence of systemic ventricular dysfunction (right ventricular ejection fraction = 35%) and severe pulmonary hypertension (pulmonary artery systolic pressure > 60 mmHg) the patient showed a maintained functional class improvement (New York Heart Association II). Also, the values of the amino-terminal fraction of B-type brain natriuretic propeptide dropped significantly (from 9787 pg/mL to 2083 pg/mL), and fewer diuretics were required. This translated into a significant improvement of the patient's quality of life, a better functional capacity, and no rehospitalizations 1 year after the procedure.

This case reinforces the role of percutaneous edge-to-edge tricuspid valve repair even in such an adverse setting as the congenitally corrected transposition of the great arteries. Very few case reports have previously described this indication,[1-3] and always in more favorable clinical situations. Our case has various technical limitations that make it extra interesting, especially the presence of a dysplastic valve with significant restriction of motion, and a large coaptation defect. Therefore, the largest device available was used to target the area with greater regurgitation (septal-posterior). Deep leaflet capture followed due to the significant bulge present even at the risk of inadvertently capturing the chordae tendineae. However, a second device was required to reduce tricuspid regurgitation significantly. Despite the inherent empiricism of the clinical situation and the unfavorable hemodynamic conditions described with severe pulmonary hypertension and severe systemic right ventricular failure, the patient improved significantly and consistently through time regardless of the lack of improvement reported in the numbers of pulmonary artery pressure and right ventricular ejection fraction. That is why we believe that the maintained reduction of tricuspid regurgitation had a clinical impact. In this sense, pulmonary hypertension[1] has been reported to improve in 1 case only, which allowed to reassess the eligibility of heart transplantation. Therefore, percutaneous edge-to-edge tricuspid valve repair should be considered an effective option in patients with congenitally corrected transposition of the great arteries who remain ineligible for heart transplantation or surgery.

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AUTHORS' CONTRIBUTIONS

A. Salinas Gallegos, and E. Pozo Osinalde: study design, and writing of the manuscript. L. Nombela-Franco, P. Jiménez Quevedo, and R. Estevez-Loureiro: management of the patient, and manuscript review. J.A. de Agustín: manuscript review.

CONFLICTS OF INTEREST

L. Nombela-Franco, and R. Estévez-Loureiro are consultors, and proctors, and have received speaking fees from Abbott Vascular, Edwards Lifesciences, and Boston Scientific.

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Clinical case

Telescoping catheter technique in percutaneous coronary intervention

Técnica de catéteres telescopados en intervencionismo coronario percutáneo

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CASE PRESENTATION

This is the case of a 69-year-old man with a past medical history of sleep apnea syndrome, and chronic lower limb ischemia syndrome grade IIB. Smoking habit was among the patient's cardiovascular risk factors reported until 2016, followed by arterial hypertension, type II diabetes mellitus, and dyslipidemia on medical therapy.

Back in January 2017, the patient was hospitalized due to second-degree atrioventricular block with implantation of a DDDR pacemaker. During hospitalization complete arrhythmia due to atrial fibrillation was confirmed that was eventually anticoagulated with rivaroxaban. In June 2017 the patient developed unstable angina with a diagnosis of severe aortic stenosis with left main coronary artery disease and 3-vessel disease. Surgical aortic valve replacement followed by revascularization with double left internal mammary artery bypass towards the left anterior descending coronary artery, and saphenous vein graft towards the second obtuse marginal branch was decided.

Currently, he complaints of angina-like symptoms during minimal exertion with a 5 to 6-month evolution, which is why cardiac catheterization was performed (prior to the procedure, the patient's informed consent was obtained anticipating the possible publication of the case for teaching purposes). This study was performed via femoral access after discarding the arm that presented some issues. It showed the native bed with left main coronary artery disease and 3-vessel disease. The difference now was that the ostium of the native left circumflex artery was occluded, the bypass of the left internal mammary artery was patent, and the bypass of the saphenous vein towards the second obtuse marginal branch showed a highly severe lesion (figure 1, figure 2, and video 1 of the supplementary data).

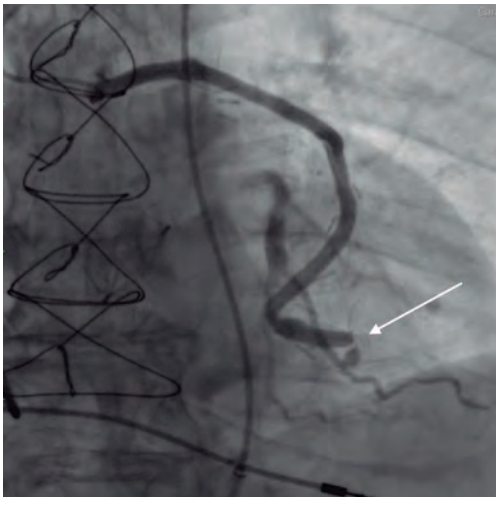

Figure 1. Focal lesion proximal to the termino-lateral anastomosis of the saphenous vein graft (white arrow).

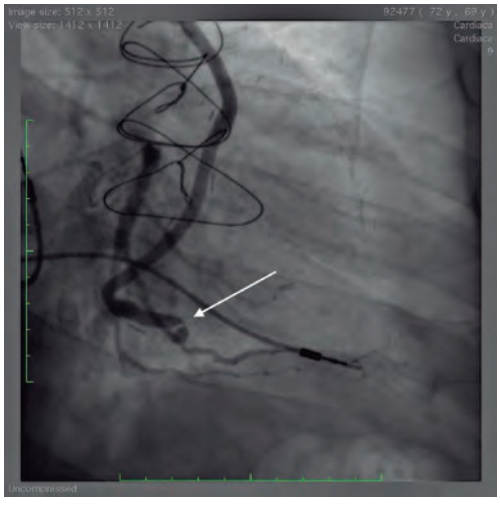

Figure 2. Focal angulated lesion of the saphenous vein graft towards the obtuse marginal branch (white arrow).

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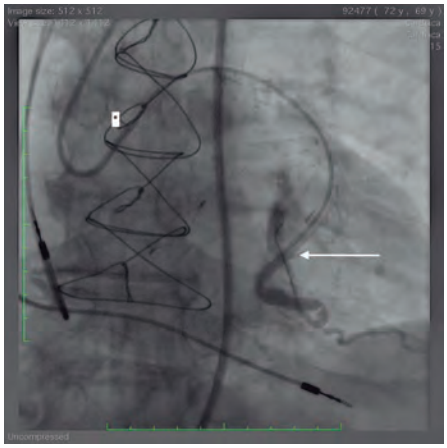

Figure 3. Note the tip of the guide extension catheter (white arrow) very close to the lesion, and the radiopaque distal part of the angioplasty guidewire inside the left circumflex artery (the asterisk corresponds to the tip of the guide catheter in the bypass ostium).

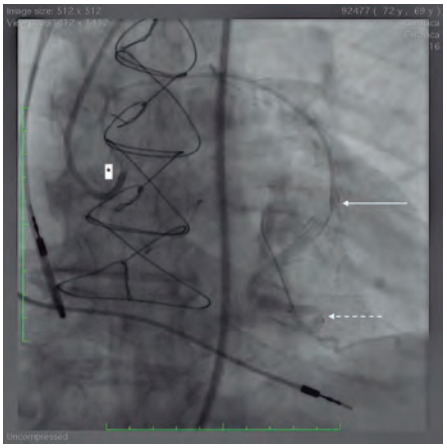

Figure 4. Note the radiopaque marks of the balloon placed in the lesion (dotted arrow). When trying to advance the device, the retreat of the radiopaque marks of the guide catheter (asterisk), and the guide extension catheter (white dotted arrow) becomes evident.

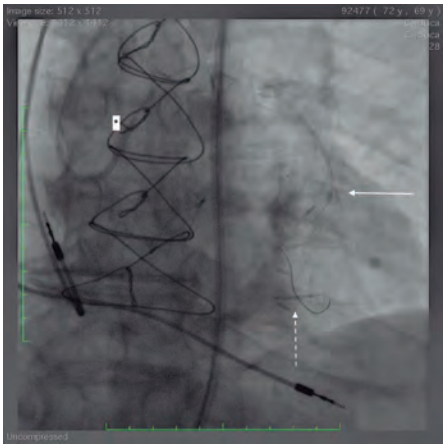

Figure 5. Inability of the Resolute Onyx zotarolimus-eluting stent (dotted arrow) to cross the lesion.

After studying the case and given the low chances of opening up the left circumflex artery native bed, it was decided to perform an interventional procedure on the saphenous vein culprit lesion. A 6-Fr AL2 guide catheter was accessed via right femoral access mounted on a SION blue Extra Support guidewire (Asahi Intecc, Japan). An attempt was made to advance a 2.5 mm x 12 mm balloon that proved unsuccessful because it never reached the lesion, which is why a 6-Fr guide extension catheter was inserted very close to the lesion (figure 3). Thanks to this support a balloon was advanced into the stenotic area and then predilated (figure 4 and video 2 of the supplementary data). However, a 3 mm × 8 mm Resolute Onyx zotarolimus-eluting stent was advanced unsuccessfully (figure 5 and video 3 of the supplementary data) even though that several maneuvers were tried including the buddy-wire technique.

Taking into consideration that, in this case, support was optimal, how could the stent be implanted into the lesion?

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

J.R. Rumoroso Cuevas wrote, edited the text of this manuscript, and provided direct medical assistance to the patient. M. Sádaba Sagredo, and A. Subinas Elorriaga supervised the manuscript and contributed to its iconography

CONFLICTS OF INTEREST

None reported.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M21000248.

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Telescoping catheter technique in percutaneous coronary intervention. How would I approach it?

Técnica de catéteres telescopados en intervencionismo coronario percutáneo. ¿Cómo lo haría?

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HOW WOULD I APPROACH IT?

The authors present an interesting and challenging case regarding percutaneous treatment, and with a very complex resolution. This is the case of a patient already surgically revascularized with significant ischemia whose revascularization option is through the bypass on which the entire territory of the left circumflex artery depends on.

At this point right now of the angioplasty where the stent cannot be crossed despite the use of the buddy-wire technique, and even though the stent was very short and had good navigability, I would try the following staged maneuvers:

1) Try to advance a high-support guidewire a little more distal inside the native vessel taking advantage of the native artery good *distal bed* so that the guidewire section with the highest support of all is placed on the curve zone. If possible, I would even bend the tip to avoid damaging the artery aware that the push forward maneuvers we'll be performing can uncontrollably displace the guidewire at any time.

2) Benefit from the balloon already crossed and the lesion already dilated to redilate the lesion with the balloon using the anchorage technique with the balloon to move the guide extension catheter forward, cross the curve, and eventually reach the lesion. With the balloon properly inflated, fix, and pull the balloon hypotube back out while the guide extension catheter is smoothly and gently advanced deep into the artery (figure 1 and figure 2).

3) Once the guide extension catheter is at lesion entry level and to secure the crossing even further, I would use the buddy-wire technique to implant the short stent we already have after examining it to discard any damage during the previous maneuvers.

Although it is true that this deep intubation technique is widely used in native coronary arteries and was described some time ago,[1,2] it should be used with extra care when dealing with bypasses, especially in the saphenous vein, to avoid dissecting or even perforating the saphenous vein bypasses that often appear degraded.

In this case the fact that the emergency of the saphenous vein bypass does not have a great proximal tortuosity and is properly aligned with the guide catheter used was an advantage.

Also, the type of guide extension catheter used should be carefully selected because there are many different ones available in the market. Some provide strength to give great support while others provide flexibility for deeper intubation without too much damage to the arteries.

FUNDING

None whatsoever.

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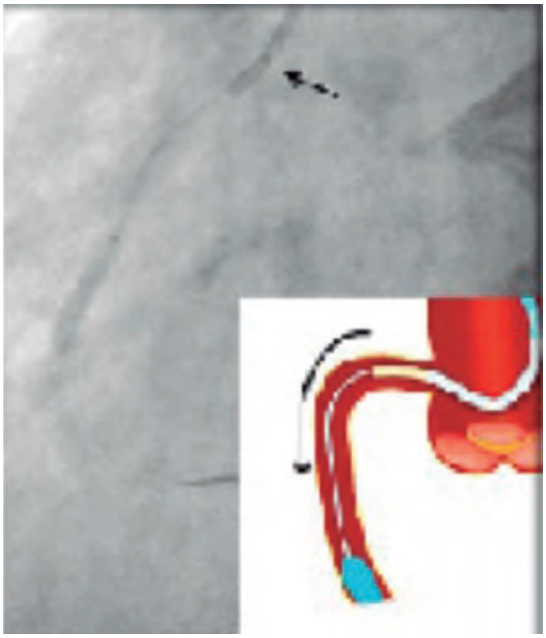

Figure 1. Example of anchorage inflating a balloon in the artery distal area and slightly pulling the hypotube back out to gently advance the guide extension catheter (in yellow).

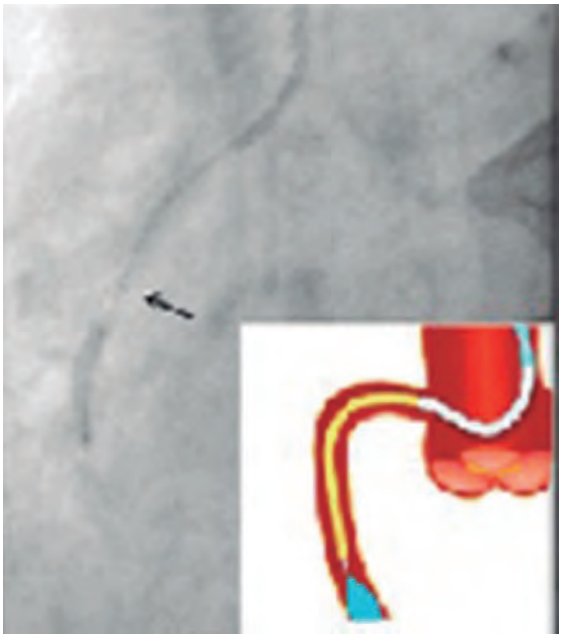

Figure 2. The guide extension catheter is advanced towards the lesion more proximal site, and the artery is deeply intubated, which increases support.

CONFLICTS OF INTEREST

None reported.

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Telescoping catheter technique in percutaneous coronary intervention. Case resolution

Técnica de catéteres telescopados en intervencionismo coronario percutáneo. Resolución

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CASE RESOLUTION

A scheduled procedure was decided. An 8-Fr 45 cm long Flexor Shuttle-SL introducer guiding sheath (Cook, United States) was inserted via femoral access again. An 8-Fr AL2 guide catheter was inserted into the ostium of the aortocoronary graft with a valve with a body shorter than usual, the FLO40XR hemostasis valve (Merit, United States). Afterwards, a 120 cm straight tip 5-Fr Heartrail ST01 guide catheter was inserted (Terumo, Japan) that was connected to a different FLO40XR valve. The SION blue Extra Support guidewire (Asahi Intecc, Japan) was advanced towards the left circumflex artery, and mounted over it, a 5-Fr GuideLiner guide extension catheter (Teleflex, United States) was advanced. The goal of this telescoping catheter system was to increase support to be able to move the stent forward (figure 1 and figure 2).

The tip of the GuideLiner catheter was placed in the most proximal region of the lesion. However, when the new 3 mm × 8 mm Resolute Onyx zotarolimus-eluting stent (mounted once again over the GuideLiner) was advanced it failed to cross the lesion (figure 3). The entire telescoping catheter system lost its position with all these crossing attempts, which is why the whole procedure had to start all over again. In the second attempt, the guidewire was advanced spontaneously towards the most distal region of the marginal branch, and when the GuideLiner was advanced it almost passed distal to the lesion (figure 4). This situation occurred because the guidewire lost the steep angulation it had as it moved proximally to the proximal left circumflex artery.

Despite of this, the same stent used before was now crossing the lesion with too many difficulties (video 1 of the supplementary data). However, it was eventually implanted in the lesion with excellent results and without causing proximal lesions (video 2 of the supplementary data and figure 5). Prior to cardiac catheterization, the patient's informed consent was obtained for the possible publication of his case for teaching purposes.

Several methods to increase support and facilitate the arrival of devices and stents into the target lesions have been described.[1] There is no doubt that long introducer sheaths, 8-Fr guide catheters, high-support guidewires, and guide extension catheters are key to perform the most complex procedures. In some cases, triple telescoping catheter systems with 2 guide extension catheters (8-Fr and 5.5-Fr GuideLiner) have been described inside an 8-Fr guide catheter with good results.[2]

In this patient, the key to success was to place a quadruple telescoping catheter system never described before to achieve the maximum passive (long introducer sheath, and 8-Fr AL2 guide catheter) and active support possible (ST01 catheter, and 5-Fr GuideLiner). Also, the better orientation of an angioplasty high-support guidewire to guarantee a more favorable access to cross the lesion without excessive angulations.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

J.R. Rumoroso Cuevas wrote, edited the text of this manuscript, and provided direct medical assistance to the patient. M. Sádaba Sagredo, and A. Subinas Elorriaga supervised the manuscript and contributed to its iconography.

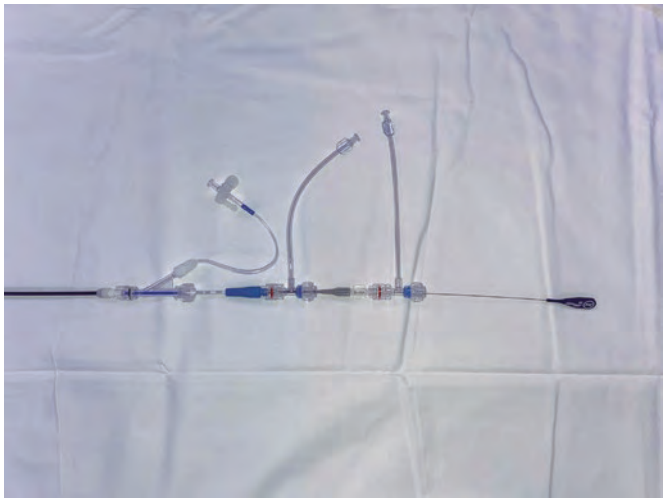

Figure 1. Arrangement of the catheters with their special valves to allow a longer usable length. The valves with the shortest bodies allow longer effective catheter lengths to reach the target lesion.

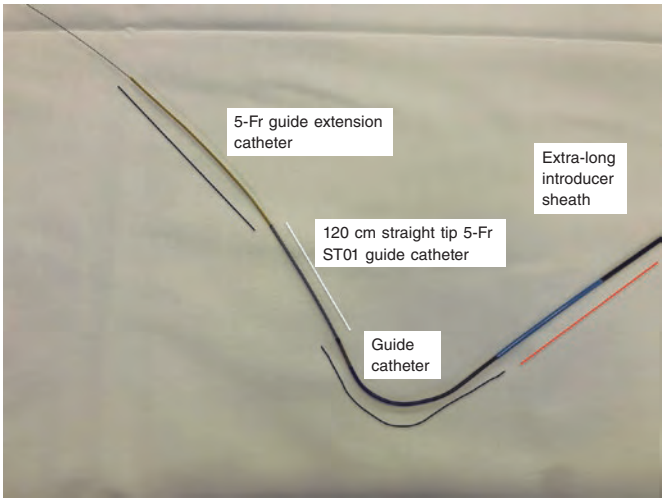

Figure 2. Quadruple telescoping catheter system mounted over the SION blue ES guidewire. The compatibility between the 5-Fr guide extension catheter and the 5-Fr ST01 guide catheter is seen here.

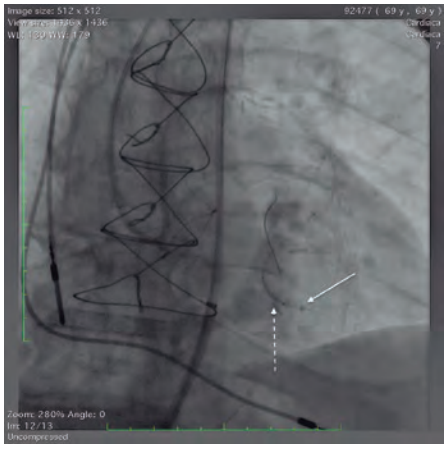

Figure 3. Note the tip of the guide catheter on the lesion proximal zone (dotted arrow), and the stent about to cross the lesion (dotted arrow).

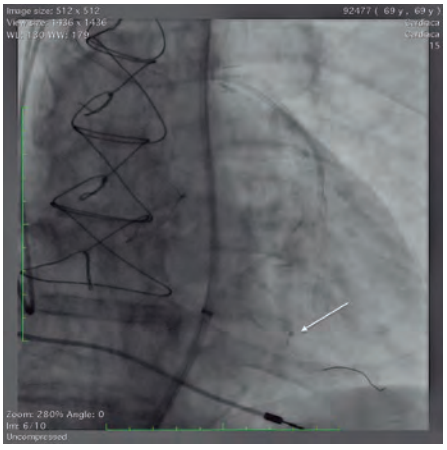

Figure 4. The guidewire advances towards the marginal branch while its more favorable position facilitates the easier advancement of the GuideLiner to cross the lesion (arrow).

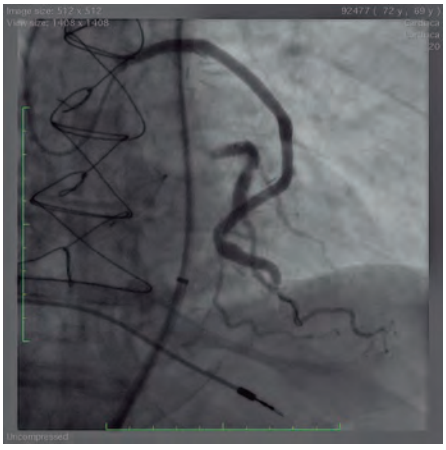

Figure 5. Result after stenting.

CONFLICTS OF INTEREST

None reported.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M21000250.

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Honeycomb-like structure: woven disease or recanalized thrombus?

Imagen en panal de abeja: ¿enfermedad en entramado o trombo recanalizado?

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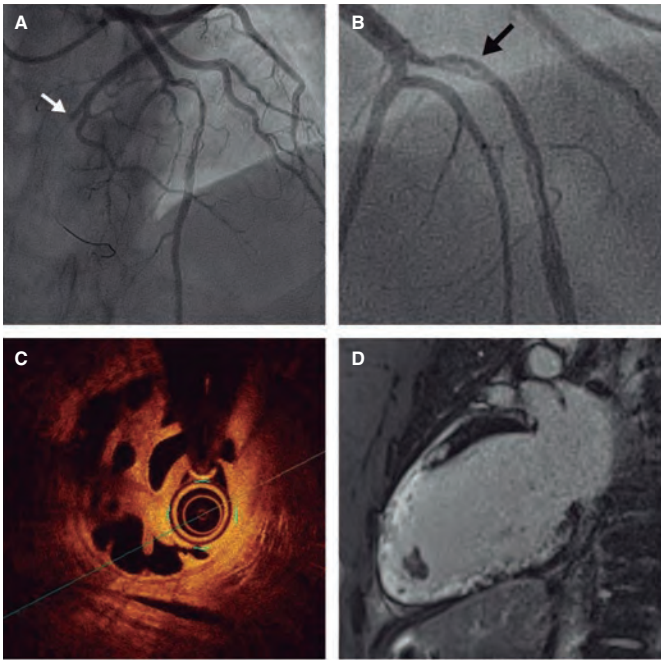

Figure 1.

This is the case of a 27-year-old male patient admitted to our hospital with acute oppressive chest pain. Clinical history was only remarkable for HIV infection under treatment with antiretroviral therapy. The electrocardiogram revealed the ST-segment elevation in leads II, III, aVF, and a QS-pattern in leads V1 to V4 suggestive of established anterior necrosis.

Coronary angiography was performed 1 hour after symptom onset revealing a total acute thrombotic occlusion of the left circumflex artery (white arrow, figure 1A), and angiographic haziness in the mid left anterior descending coronary artery (black arrow, figure 1B). The circumflex artery was treated with thrombectomy and angioplasty with drug-eluting stent implantation. The optical coherence tomography performed on the left anterior descending coronary artery revealed a honeycomb-like structure with multiple intraluminal channels. (figure 1C, video 1 of the supplementary data). The MRI confirmed the presence of moderate left ventricular systolic dysfunction (left ventricular ejection fraction = 45%), established anterior, anteroseptal, apical, and inferoseptal transmural necrosis without myocardial viability, and apical thrombi. (figure 1D). Dyslipidemia and thrombophilia were investigated and discarded. The patient was discharged on triple antithrombotic therapy. Informed consent was obtained from the patient for case report purposes.

Woven coronary artery disease is an extremely rare congenital anomaly in which the coronary artery branches into multiple thin channels that merge once again to form a normal vessel. The optical coherence tomography is crucial here for the differential diagnosis of thrombotic recanalization, dissection or chronic occlusion with bridging collaterals. In woven disease, histopathology and intravascular imaging have

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reveal the presence of elastic tunicae and endothelial coating. In our case, despite the patient's young age, the presentation of ST-segment elevation myocardial infarction in a different coronary territory, the electrocardiogram changes suggestive of anterior necrosis, the magnetic resonance imaging findings, and the intravascular imaging all confirmed thrombotic recanalization.

FUNDING

None reported.

AUTHORS' CONTRIBUTIONS

All authors have participated in the writing of this article, edition, and graphic composition of the figures and video. All authors approved the final version of this manuscript.

CONFLICTS OF INTEREST

None reported.

SUPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M21000226.

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Acute failure of cutting balloon fenestration in spontaneous coronary artery dissection

Fracaso agudo de fenestración con balón de corte en disección coronaria espontánea

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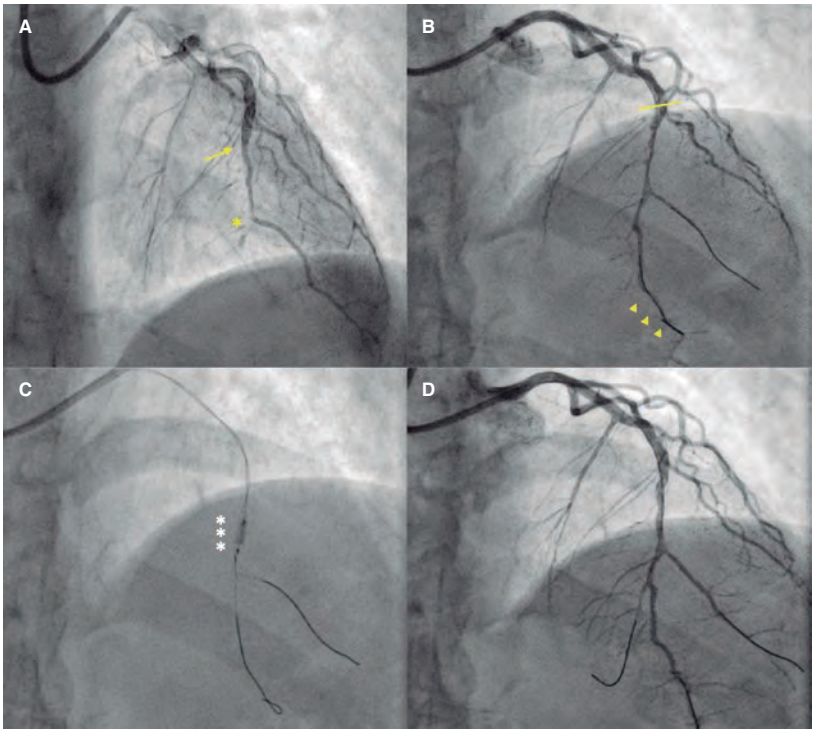

Figure 1.

We present the case of a 42-year-old woman admitted due to ST-segment elevation acute coronary syndrome. The coronary angiography revealed the presence of an occluded mid-distal left anterior descending coronary artery (LAD) (figure 1A, asterisk) with an image suggestive of intramural hematoma (IMH) consistent with spontaneous coronary artery dissection (figure 1A, arrow). Guidewires were passed through the distal and diagonal LAD that resulted in flow recovery (figure 1B, line and arrowheads outlining the IMH). The intravascular ultrasound (IVUS) confirmed the presence of a large 25 cm long IMH (figure 2A,D). After dilatation with a 2.0 mm/6 mm cutting balloon (Wolverine, Boston Scientific, United States) (figure 1C, asterisks) flow improved leaving a mild residual stenosis (figure 1D). After a few minutes the retention of contrast in the LAD was confirmed (figure 3A, ellipse) followed by ischemic changes on the electrocardiogram. The angiography revealed the presence of 2 regions of critical stenosis with aggravated distal flow abnormalities (figure 3B, lines outlining the IMH, arrowheads showing the stenotic regions). A 2.25 mm/33 mm drug-eluting stent was implanted (Ultimaster Tansei, Terumo, Japan) (figure 3C, asterisks) and later dilated up to 2.75 mm with excellent angiographic (figure 3D) and IVUS results (figure 2E,F). The entire procedure is summarized on video 1 of the supplementary data.

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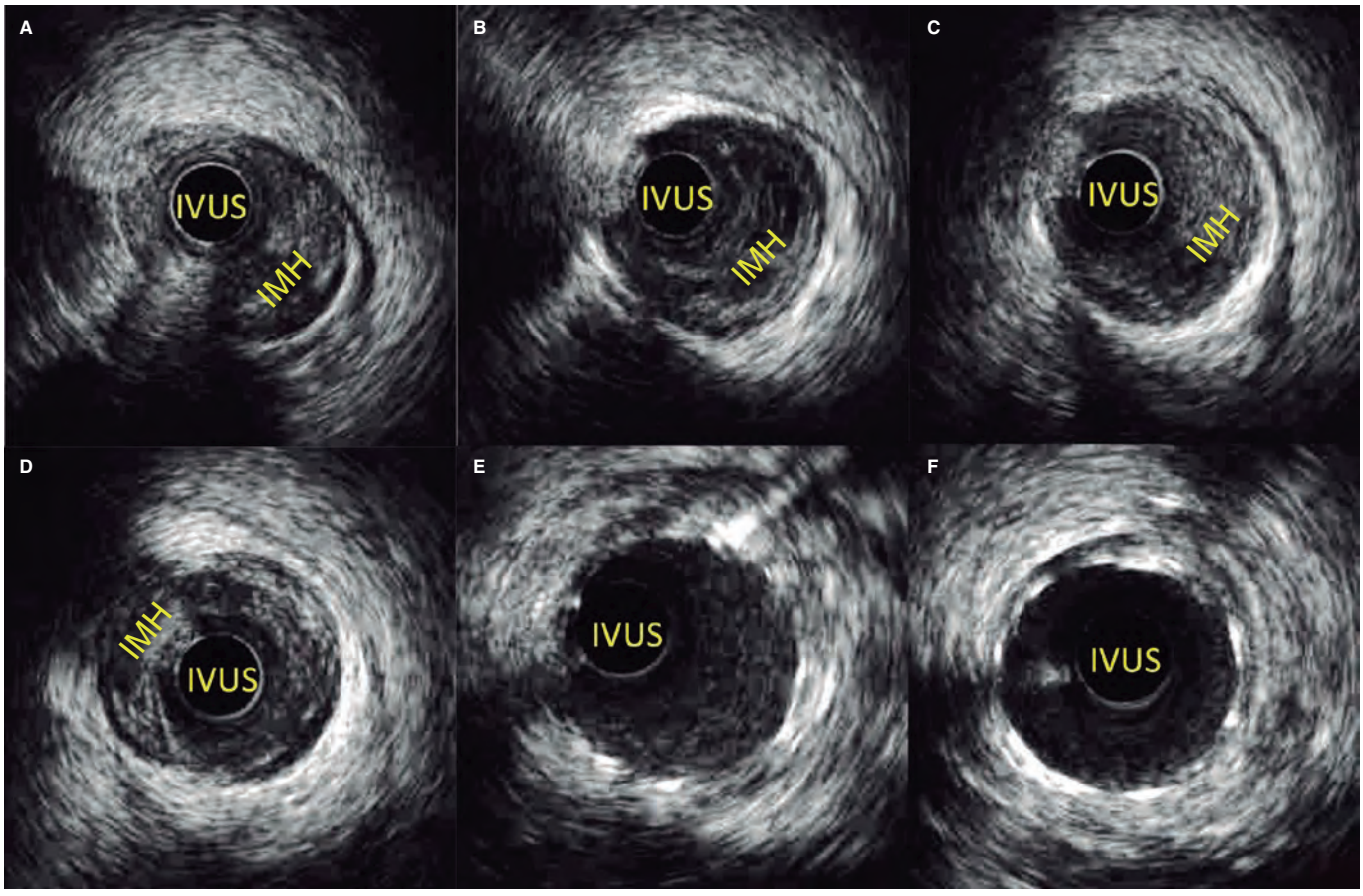

Figure 2.

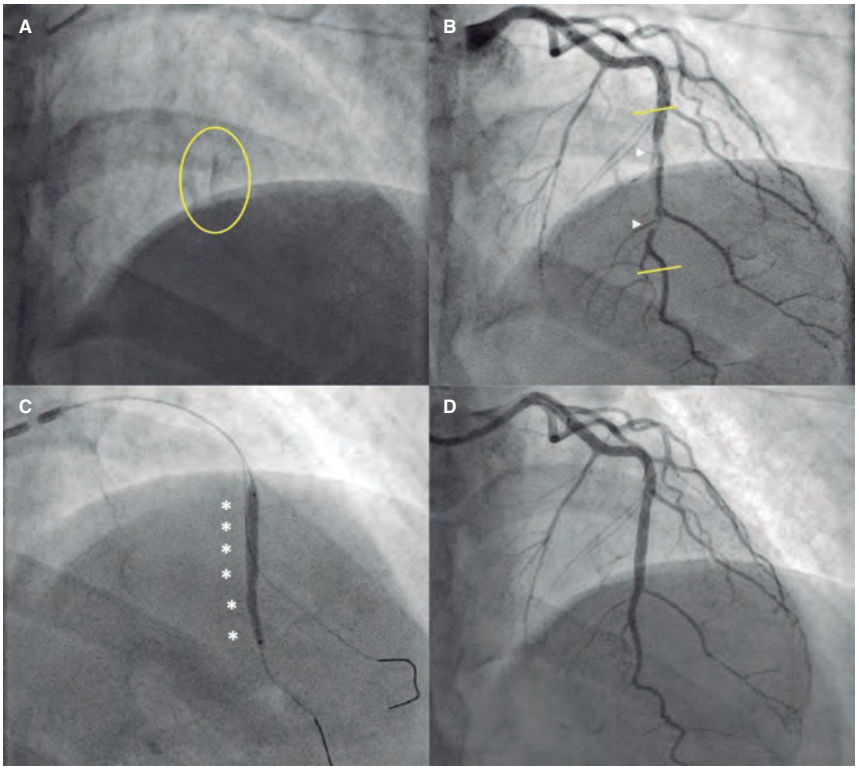

Figure 3.

The patient's informed consent case was obtained before publishing the case.

We reported our experience on the isolated use of a cutting balloon during percutaneous coronary intervention to treat spontaneous coronary artery dissection to generate the fenestration of the IMH and, eventually, reduce the possible risk of spreading. The use of the cutting balloon before stent implantation can also prevent the spread of IMH after implantation. This case illustrates the fact that, sometimes, the totally unpredictable evolution of the isolated strategy makes stent implantation necessary to guarantee good distal flow and prevent coronary artery re-occlusion.

FUNDING

None.

AUTHORS' CONTRIBUTIONS

M. Vicente, and García-Guimaraes designed the study and wrote the manuscript. N. Salvatella, A. Aparisi, A. Negrete, and B. Vaquerizo performed the critical review of the manuscript.

CONFLICTS OF INTEREST

The authors declared no conflicts of interest whatsoever.

SUPPLEMENTARY DATA

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Ischemia in single right coronary artery

Isquemia en arteria coronaria derecha única

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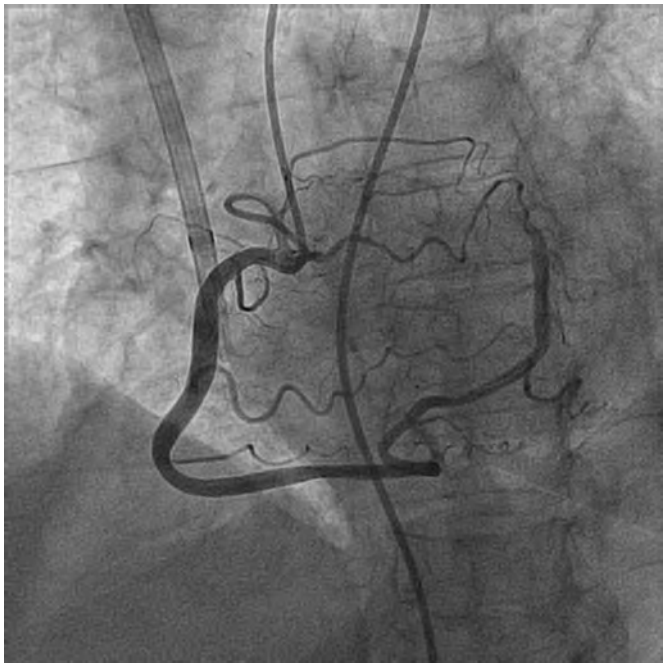

Figure 1.

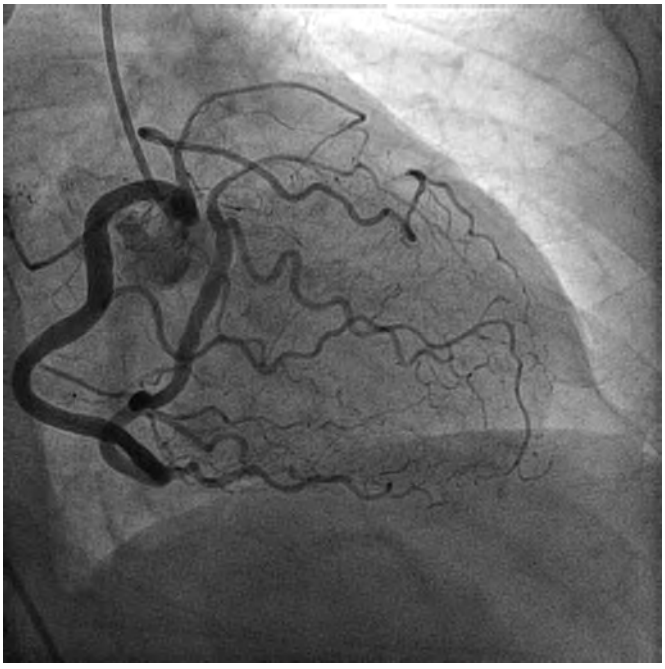

Figure 2.

This is the case of a 77-year-old woman with hypertension, dyslipidemia, and stage V chronic kidney disease. While on hemodialysis she experiences precordial pain due to paroxysmal atrial fibrillation with rapid ventricular response. The electrocardiogram shows widespread ST-segment depression. The blood tests confirm the presence of slightly elevated ultrasensitive troponin I levels later showing an ascending and descending curve suggestive of acute coronary syndrome. A coronary angiography is indicated after these findings.

The coronary angiography shows a single right coronary artery (figure 1) running through the atrioventricular sulcus and generating branches with perfusion to all myocardial territories of the left and right ventricles (figure 2 and video of the supplementary data).

The prevalence of single right coronary artery is between 0.024% and 0.066%; the single right coronary artery is, actually, one of the rarest variants.

In these patients, flow runs through a system with a large sequence of serial resistances. Based on these findings, we could argue that the perfusion of medioapical segments would be in a situation of «relative» ischemia compared to the rest. This would exacerbate in situations of greater myocardial demand as in tachyarrhythmias.

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Although cases of chest pain or angina have been reported in patients with this anomaly who did not have coronary atherosclerosis, it is difficult to establish a causal correlation between the angiographic finding and the clinical signs. Coronary microcirculation was not assessed either, which is why the pathophysiological mechanism suggested is pure speculation.

The patient's written informed consent was obtained before publishing her case.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

C. Garilleti, and J. M de la Torre-Hernández drafted the manuscript. A. Gil Ongay conducted the critical review of its content and gave his final approval.

CONFLICTS OF INTEREST

J. M de la Torre-Hernández is the editor-in-chief of *REC: Interventional Cardiology*; the journal's editorial procedure to ensure impartial handling of the manuscript has been followed. The remaining authors declared no conflicts of interest whatsoever.

SUPPLEMENTARY DATA

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Correction in article by Sanz-Sánchez et al. "Single or dual antiplatelet therapy after transcatheter aortic valve implantation. A meta-analysis of randomized controlled trials", *REC Interv Cardiol*. 2021;3:175-181

Corrección en el artículo de Sanz-Sánchez et al., «Tratamiento antiagregante plaquetario único o doble tras implante percutáneo de válvula aórtica. Metanálisis de ensayos clínicos aleatorizados», REC Interv Cardiol. 2021;3:175-181

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In the article entitled "Single or dual antiplatelet therapy after transcatheter aortic valve implantation. A meta-analysis of randomized controlled trials" an error has been found in the translation of the article into Spanish language. The first sentence of section "What is known about the topic?" reads: "Ischemic and bleeding complications are rare after TAVI and can be life-threatening"; the correct phrase should have been "Ischemic and bleeding complications are not rare after TAVI and can be life-threatening".

This correction has been published on the electronic version of the article at https://doi.org/10.24875/RECICE.M21000210.

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